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VOLUME 63 NUMBER 5

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MAY 1950

PUBLISHED MONTHLY BY AMERICAN MEDICAL ASSOCIATION, 535 NORTH DEARBORN STREET, CHICAGO 10, ILLINOIS. ANNUAL SUBSCRIPTION, $12.00

Entered as Second Class Matter Jan. 7, 1919, at the Postoffice at Chicago, Under the Act of Congress of March 3, 1879

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GARGOYLISM (LIPOCHONDRODYSTROPHY)

A Study of Ten Cases, with Emphasis on the Formes Frustes of the Disease

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THIELLS, N. Y.

THE CONDITION known as gargoylism (lipochondrodystrophy, or the Hunter-Hurler syndrome) shows such striking clinical pathologic and etiologic features that it may be considered one of the best defined disease entities of all types of mental defect. Yet the study of this condition has not received the attention it deserves. To be sure, typical instances of the disease are easily recognized, and many have been reported in the literature; but cases with incomplete and less striking clinical manifestations often escape recognition. These formes frustes, which are perhaps more numerous than the typical forms of the disease, show interesting clinical and pathologic aspects.

It is the purpose of this paper to contribute to the knowledge of gargoylism by describing a series of 10 cases. In the first section, 3 typical instances of the complete form of the disease will be briefly reported and the main clinical features of the disease reviewed. The second section will be devoted to the clinical study of formes frustes. Seven cases of this type will be described and the diagnostic criteria outlined. In the third section, the pathologic findings in 2 cases of formes frustes will be reported and some pathologic aspects of the disease commented on. Finally, in the last section, the etiology of gargoylism will be briefly discussed. In the appendix, the main features of some 150 cases which have been described in the literature are tabulated.

"COMPLETE FORMS" OF GARGOYLISM

CASE 1.—V. O., a white girl, was admitted to Letchworth Village at the age of 10 years. The family history, which included fourteen members of two generations of mixed Irish-English descent, showed no other instances of the disease. There was no consanguinity. The patient was the only child. Delivery was normal and followed an uneventful gestation. The weight at birth was 3,500 Gm. During the first year of life physical development proceeded regularly, but at the sixth month it was noted that the mouth was large and the root of the nose somewhat depressed. At 1 year of age mental retardation was apparent. Walking and talking were delayed, but at 2 years of age she was able to say many words and at 3 years she would speak in short sentences. During these years the abnormality of the facial

From the Research Department, New York State Department of Mental Hygiene, Letchworth Village.

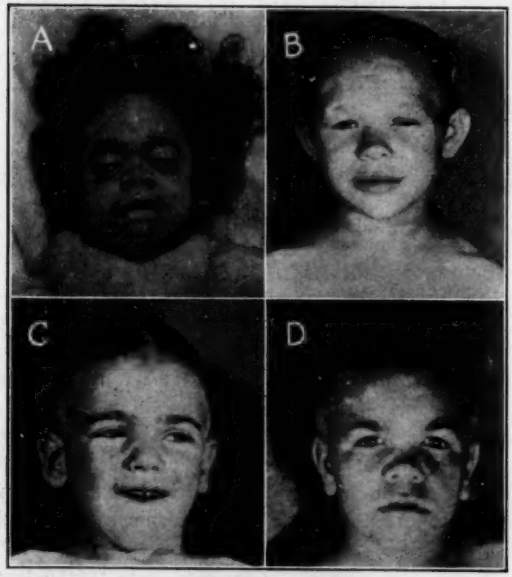

Fig. 1.—The face in typical gargoylism (*A*, case 1) and in formes frustes (*B*, case 7; *C*, case 8, and *D*, case 9).

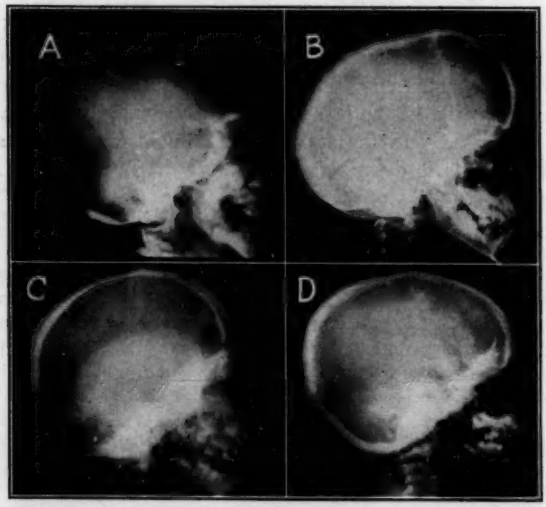

Fig. 2.—Roentgenograms of the skull in cases of gargoylism: *A*, case 1; *B*, case 4; *C*, case 6, and *D*, case 8.

features became more pronounced and oxycephaly was apparent. At 4 years of age bilateral clouding of the cornea was first noted. This progressed slowly until three years later both corneas showed a diffuse "milky" opacity. Mental deterioration began at the age of 4 years and progressed gradually, reaching an extreme degree of idiocy in about two years. Speech was the first to disappear, followed by lack of

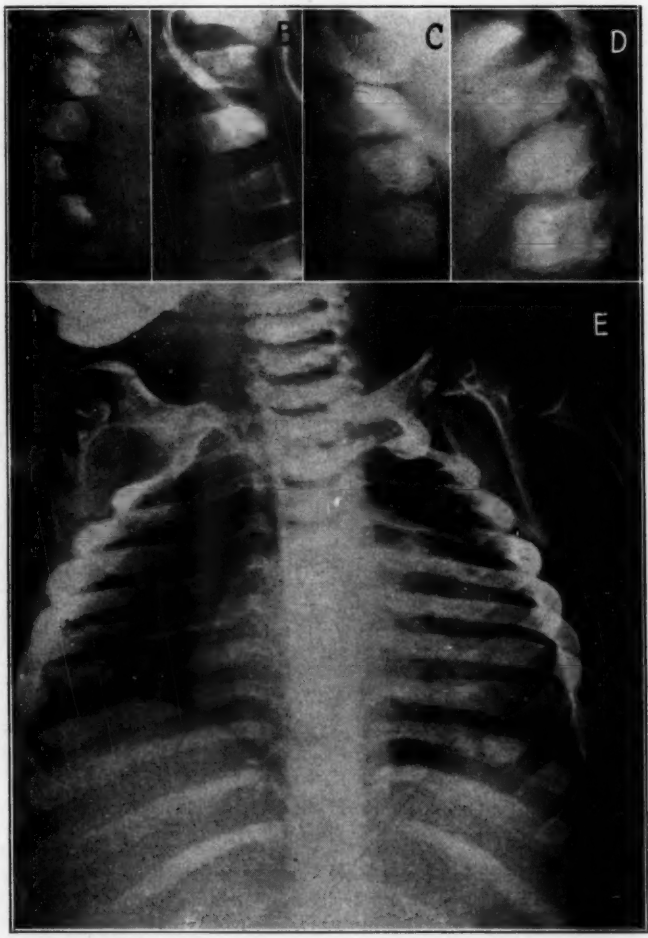

Fig. 3.—Roentgenograms of the lumbar portion of the spine showing various deformities of the vertebral bodies: *A*, case 1; *B*, case 7; *C*, case 8, and *D*, case 9. *E*, case 1, roentgenogram of the chest, showing enlarged, "spatulated" ribs.

interest and apathy. At 5 years she was unable to walk unassisted, and a year later she was constantly bedridden, had to be fed and reacted only to strong stimuli, leading a purely vegetative existence.

Examination on her admission to the Village showed an undersized (105 cm.), strikingly deformed idiot child with an intelligence quotient below 5. The face showed the typical unhuman aspect of gargoylism (fig. 1*A*). The forehead was bulging; the eyebrows were bushy; the eyes were protruding and set widely apart. The corneas were whitish, and the fundi were not visible on ophthalmoscopic examination. The root of the nose was depressed; the nares were flaring, and the malar bones were prominent. The mouth was wide; the tongue and lips were thick. All the teeth were missing. The head was large (62 cm. in circumference), acrocephalic and scaphocephalic (fig. 2*A*). The sella turcica was flat and twice

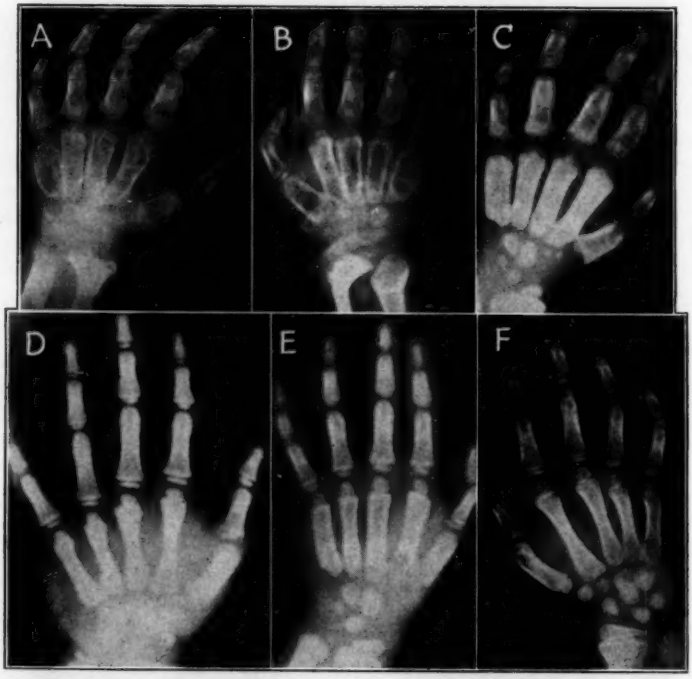

Fig. 4.—Roentgenograms of the hands showing various degrees of deformities: *A* and *B*, case 1; *C*, case 6; *D*, case 7; *E*, case 8, and *F*, case 10.

the normal length. The neck was short, and the head appeared to rest on the shoulders. There was pronounced kyphosis of the dorsolumbar region. The vertebral bodies appeared irregular in shape. The most pronounced alteration was seen in the second lumbar vertebra, which was smaller than normal and wedge shaped, and showed a beaklike formation in its anterior aspect (fig. 3*A*). The chest was somewhat deformed, the diameter of the lower third being wider than that of the upper third. The ribs were large, flat and spadelike; the intercostal spaces were reduced in width (fig. 3 *E*). The abdomen was protruding, and a large umbilical hernia was present. The liver and spleen were greatly enlarged, the

lower margin of the liver being felt at the umbilical line and the inferior pole of the spleen at the iliac crest. Both upper and lower extremities showed deformities of the epiphysial outlines. The diaphyses were shorter than normal and distorted. The hands were short and plump and clawlike in appearance. The characteristic cone-shaped aspect of the metacarpal bones and phalanges was present (fig. 4*A, B*).

Neurologic examination revealed motor paralysis extending to the muscles of the extremities, trunk and neck; muscular tonicity was increased, and a Babinski sign was present bilaterally.

A series of laboratory tests, including examinations of the urine, blood and spinal fluid revealed no significant changes, the only abnormality being a positive reaction in the thymol turbidity test.

The electroencephalogram showed slow waves (3 to 4 per second) of high voltage (50 to 60 microvolts) in all leads. There was no alpha activity.

Death occurred suddenly with the manifestations of acute cardiac failure. Permission for autopsy was not obtained.

CASE 2.—M. A., a white girl, was admitted to Letchworth Village at the age of 5 years. The family history, which included three generations of mixed Swiss-German extraction, showed no other cases of mental defect or bony deformities and no consanguineous marriages. The patient had only one sib, who was similarly affected (case 3). Birth was normal, and early development had been normal until the age of 7 months, when slight kyphosis was observed. Roentgenologic examination showed a wedge-shaped second lumbar vertebra with beaked deformity of the vertebral body, as described in case 1. The facial features of the disease were already apparent at the age of 1 year, and somewhat later the mental defect was obvious. Whether deterioration had occurred was not clear.

The period between the ages of 2 and 5 years was characterized by slowly progressing distortion of the facial features, skull and long bones and by failure of mental development.

Examination on admission showed an undersized (height, 90 cm.) idiot girl (intelligence quotient, 20), with a large head (63 cm. in circumference), hypertelorism, saddle nose, large mouth and thick lips. The teeth were few, irregularly spaced, misshapen and carious. The corneas were diffusely opaque and the eyes bulging. The sella was enlarged and flat. The neck was short; there was pronounced kyphosis of the dorsolumbar region, due to the vertebral alteration aforementioned. The ribs were ribbon-like. The abdomen was protruding, and a large umbilical hernia was present. The liver was palpable 4 inches (10 cm.) below the costal margin, and the inferior pole of the spleen reached the level of the iliac crest. The limbs were short and distorted. Limitation of movements at the elbows and wrists was pronounced, and both hands were short, broad and clawlike in appearance. The deformities of the bones were in all respects similar to those observed in case 1. The patient was unable to stand or walk; motor deficit was present in all limbs; the deep reflexes were increased, and a Babinski sign was present bilaterally.

Laboratory examinations showed no abnormalities.

The patient died at the age of 6 years, of bronchopneumonia and cardiac failure. Permission for autopsy was not obtained.

CASE 3.—M. R., an older brother of the patient in case 2, was never admitted to the institution. He was, however, examined repeatedly by various investigators, and complete medical records were available. Like his sister's, birth and early development were normal. The first manifestations of the disease did not occur until the age of 2 years, when kyphosis was noted and abnormalities of the verte-

brae, similar to those in case 2 were observed. At this time no marked intellectual defect was present, and even later his mental level was noticeably higher than that of his sib, although with the progress of the disease mental deficiency became well established. At the age of 5 years, the clinical picture was that of complete gargoylism, with enlarged head, characteristic facial features, dwarfism and bony deformities. Both corneas were clouded and the liver and spleen enlarged. The roentgenologic findings were almost identical to those for the younger sib. Laboratory tests showed no abnormalities.

The patient died at the age of 7 years, apparently of sudden heart failure. Autopsy was not performed.

COMMENT

These 3 patients showed such a striking combination of clinical features that the diagnosis involved only a superficial examination. The clinical features may be grouped under four headings: mental defect, deformities of bone, enlargement of the liver and spleen and, finally, corneal opacities.

1. The mental defect was severe in the first 2 patients, who were classified as idiots, and somewhat less advanced in the third patient. That wide variations in mental deficiency, from idiocy to moronism, occur in gargoylism is apparent from a survey of the published cases, although the majority of typical cases show severe intellectual deficiency. It is doubtful whether entirely normal mentality can be present in the complete form, although Meyer and Okner [1] and Nöller [2] stated, without details, that their patients were not defective. In all the cases described, the patients of Ellis [3] and Liebenam [4] had probably the most nearly normal mentality. Normal intelligence may be present, however, with the formes frustes, as described in the next section. One may conclude, therefore, that mental defect is an integral part of the clinical picture of complete gargoylism.

Worthy of note is the progressive intellectual deterioration in case 1 and, to a lesser extent, in case 3. As a matter of fact, in about 15 cases recorded in the literature, there was noted a regression of intellectual abilities from the second or third year onward with, occasionally, a normal mentality up to this age. Such a progression of mental symptoms is not unlike that seen as a rule in juvenile amaurotic idiocy.

Mental deficiency is often accompanied with neurologic signs of damage to the central nervous system. In the present cases, motor

1. Meyer, S. J., and Okner, H. B.: Dysostosis Multiplex with Special Reference to Ocular Findings, Am. J. Ophth. **22**:713, 1939.

2. Nöller, F.: Dysostosis multiplex (Hurler) und verwandte Krankheitsbilder, Deutsche Ztschr. f. Chir. **258**:259, 1943.

3. Ellis, R. W. B.: Report of an Additional Case of Gargoylism, Arch. Dis. Childhood **15**:215, 1940.

4. Liebenam, L.: Beitrag zur Dysostosis multiplex, Ztschr. f. Kinderh. **59**:91, 1937.

paralysis, increase of muscular tonus and the Babinski sign were observed. With the progressing mental deterioration an increase of neurologic manifestations is usually apparent.

2. Multiple and varying deformities of bone were conspicuous in these cases. The patients were dwarfed. The face showed the characteristic grotesque appearance, which is due to a combination of prominent frontal bones, hypertelorism, depressed nose, high malar bones, a large mouth and thick lips. Because of the facial features, patients with complete gargoylism show a striking similarity to one another, a fact well exemplified in the present cases. Acrocephaly, scaphocephaly and macrocephaly were the deformities of the skull encountered in these cases. Worthy of note was the elongation of the sella turcica. The vertebrae showed irregularities of outline and variation in size. Of considerable diagnostic significance was the wedge-shaped appearance of one of the lumbar vertebrae, which exhibited a peculiar hooklike process in its anterior aspect. This deformity resulted in pronounced kyphosis. Characteristic also were the ribbon-like shape of the ribs, which tapered at both ends, and the multiple bony deformities of the limbs. The latter consisted of abnormal shortness and irregular thickness of the long bones, particularly the ulna and radius; poorly formed articulating surfaces, observed at best in the mandibular fossae and the acetabula, and, finally, the claw-shaped, stubby hands, with a "cone-shaped" aspect of the phalanges in roentgenograms.

These characteristic bony changes, with minor variations, were present in all cases of the complete form of the disease described in the literature.

3. Enlargement of both the liver and the spleen was conspicuous in the cases described here. It appears to have been present in most reported cases of complete gargoylism which were the object of detailed study.

4. Opacities of the cornea were present in the present 3 cases. They appeared as diffuse clouding of the deep layers of the cornea, conferring to the eye a striking milky appearance. This sign is in itself pathognomonic of gargoylism, having been encountered in no other condition.

Laboratory tests in these 3 cases included routine examinations of the urine, blood and spinal fluid and determinations of the cholesterol, phosphorus, phosphatases and calcium of the blood serum. In case 1, a complete determination of the blood lipid was made, according to the technics outlined by Tannhauser and Schmidt,[5] with normal results. One may conclude, therefore, that in gargoylism there are no characteristic alterations of the lipid content of the blood.[6]

5. Tannhauser, S. J., and Schmidt, G.: Lipins and Lipidoses, Physiol. Rev. **26**:275, 1946.

These four groups of symptoms and signs are present in the complete forms of gargoylism. The clinical delineation of the disease, therefore, is clearcut, and the physical appearance is striking enough to betray the diagnosis immediately.

FORMES FRUSTES OF GARGOYLISM

That the diagnosis of gargoylism is possible in the absence of one or more of the clinical manifestations outlined in the preceding section is apparent from a perusal of the literature, almost two thirds of the recorded cases being symptomatologically incomplete in some respect. Since gargoylism presents itself under varied clinical manifestations, the problem arises as to the recognition of incomplete, atypical variants and their relation to the complete forms of the disease. With a view to contributing to the solution of this problem, the following 7 cases are presented as instances of formes frustes of gargoylism.

CASE 4.—H. M., a white girl, was admitted to Letchworth Village at the age of 6 years. The family was of German and English extraction, and there had been no consanguineous marriages. Both parents were in good physical health and of above average intelligence. A brother, first in line of birth, was normal both physically and mentally. The patient had an older sister, who is case 5 of the present series.

The birth and early development were normal. The child sat up at 4 months of age, walked at 12 months and talked in short sentences at 18 months, and toilet habits were established without difficulty. Normal physical and mental development continued to the age of 4 years, when she appeared alert mentally, conversed freely and showed much social interest. It was at this time that a change in behavior was first noted. She began to lose interest in playmates and toys, and shortly thereafter her speech became hesitant and stumbling. The mental deterioration progressed gradually. At the age of 5 years she had lost all verbal expression and was unable to obey even simple commands. Motility was still unimpaired, and neurologic examination showed no abnormalities. The pneumoencephalographic examination and routine laboratory tests revealed nothing abnormal. Some degree of scaphocephaly was present, and her face showed a slightly "cretinoid" appearance.

On her admission to the hospital, at the age of 6 years, the patient appeared as a slightly undersized (95 cm.) idiot (intelligence quotient 20). The skull was larger than normal (61 cm. in circumference); the bones of the vault were thick and spongy, and the sella was somewhat elongated and flat (fig. 2*B*). Scaphocephaly was marked, and the frontal bosses were prominent. The face had a cretinoid appearance, the root of the nose being slightly depressed and the lips and tongue somewhat coarser than normal. There was no clouding of the cornea. The hair was coarse but abundant, and the eyebrows were well developed. Deformities of the spine were not present, but some of the vertebral bodies were irregular in outline. The ribs on roentgenologic examination had a spatula-like appearance. The limbs were normal, and there was no limitation of movements. However, the hands were broader and shorter than normal, and the phalanges had a cone-shaped configuration. Neurologically, there was mild spastic paresis of the lower extremities, with a Babinski sign bilaterally.

During the following years, spasticity increased gradually but slowly, extending to the upper limbs. Progressive enlargement of the spleen and liver was noted. The gait became increasingly difficult, and during the last year the patient was bedridden, leading a purely vegetative existence. No clouding of the cornea was apparent at any time. Death occurred at the age of 11 years, of bronchopneumonia.

Autopsy, which is reported in the next section, showed lesions typical of gargoylism.

CASE 5.—H. A., older sister of the patient in case 4, was not hospitalized. She was born of a normal delivery after an uneventful gestation. Her early development showed no conspicuous abnormalities, although she showed some retardation in walking (at the age of 14 months) and in talking (at 20 months). However, at the age of 4 years she appeared mentally normal in the opinion of untrained, but reliable and intelligent, observers. From the age of 4 years onward progressive mental deterioration was observed. She gradually lost her power of speech and became listless and uninterested. At the age of 5 years she was bedridden, being unable to stand or walk, and showed episodes of irritability and purposeless motor overactivity. Examination at the age of 6 years showed facial features very similar to those of her younger sister; the face was unusually broad, the root of the nose somewhat depressed and the mouth large with thick lips. The deformities of the skull were also similar to those described in case 4. There was no clouding of the cornea. The abdomen was protruding, and both the liver and the spleen were enlarged. No deformity of the spine was noted, but roentgenologic examination was not performed.

The patient died at 6 years of age. Autopsy was not available.

CASE 6.—T. R., a white boy, was admitted to Letchworth Village at the age of 6 years with the diagnosis of cretinism. The family history, which included three generations of Norwegian paternal and English maternal ancestry, revealed no consanguinity or evidence of mental disease on either side of the family. The sibship consisted of three living members. An older brother was mentally retarded but could not be examined, and there was insufficient information for a diagnosis of gargoylism. A younger brother was normal. One sib died in early infancy of unknown cause.

The patient's birth was normal and followed an uneventful gestation. Development was retarded; he sat alone at 9 months, began to walk at 14 months and said a few words at 2 years, but complete sentences were formed much later. The physical facial characteristics present on admission had been noted from early infancy.

On admission, the patient appeared as an undersized (height, 100 cm.), low grade imbecile (intelligence quotient, 29). The skull, 51 cm. in circumference (fig. 2*C*), was somewhat acrocephalic, and the frontal bosses were prominent. The sella was slightly enlarged. The hair was abundant. The nose was large with flaring nostrils and depressed bridge; the cheek bones were high; the mouth was large with puffy lips and large tongue. There was no clouding of the corneas. Mild kyphosis was present. The outlines of several vertebrae were irregular; the first lumbar vertebra was small and wedge shaped. The ribs were spadelike. The liver and spleen were within normal limits. The external genitalia appeared hypotrophic. There was little limitation in the movements of the limbs, but the epiphyses of the humerus and femur were irregular in outline and the hands showed short and large phalanges, which were of cone-shaped configuration (fig. 4*C*).

Laboratory examinations were noncontributory.

Mental deterioration was slowly progressive during the following years, the intelligence quotient dropping from 29 to below 10. In addition, progressive spastic

paralysis developed. At the age of 12 years the patient was bedridden and exhibited tetraplegia in forced flexion, increased deep reflexes and signs of pyramidal involvement. A roentgenogram of the skull showed evidence of marked internal hydrocephalus.

The patient died at 15 years of age, of pneumonia. Autopsy, reported in the next section, showed lesions of the brain characteristic of gargoylism.

Case 7.—O. H., a white boy, was admitted to Letchworth Village at 5 years of age. The family was of mixed Swedish and German extraction, and information was available concerning the four grandparents, three uncles and six first cousins of the patient. There were no cases of mental defect or bony deformities and no consanguinity. The patient, fourth in the line of birth, had four normal sibs.

Gestation and birth were normal, and early development was normal until the age of 10 months. At this time some mental retardation was noted, which was attributed to an attack of pertussis at 9 months of age. During this acute illness, however, no evidence of involvement of the central nervous system had been observed. At the age of 1 year he was given prolonged thyroid treatment, without apparent benefit. He sat up at 2 years of age, but never walked or talked and was not toilet trained when admitted to the institution. A diagnosis of cretinism was made at the age of 2 years because of the "cretinoid face."

On admission, he appeared as a somewhat underdeveloped (height, 88 cm.) low grade imbecile child (intelligence quotient, 24). The head was 51 cm. in circumference and was dolichocephalic and somewhat scaphocephalic. The face was peculiar (fig. 1 *B*), with a low hair line, prominent frontal bosses, pug nose and prominent maxillas. The mouth was large and the lips were thick. The neck was short, the thorax normal and the abdomen protruding. The liver was palpable 4 cm. below the costal margin. A small inguinal hernia was present. There was slight kyphosis of the lumbar portion of the spine. The lumbar vertebrae were small and irregular in outline. The second lumbar vertebra was the most affected, being reduced in size and showing a hooklike process in its anterior aspect (fig. 3 *B*). The extremities appeared normal, but there was some limitation in the extension of the elbows. The hands, although not short or pudgy, showed a slightly cone-shaped configuration of the phalanges (fig. 4 *D*). Neurologic examination revealed an essentially normal condition. Laboratory data showed nothing of significance. An electroencephalogram showed abnormally slow activity, diffuse throughout the record.

There was no mental deterioration during ten years of hospitalization.

Case 8.—H. P., a white boy, was admitted to Letchworth Village at 5 years of age. The family was of Netherland origin, with no history of consanguinity. Both parents were healthy and came of large families, in which there was no record of mental defect. The patient had a normal younger brother. Birth was prolonged and difficult. Low forceps were used, but no anoxia or injury was observed. The weight at birth was 4,200 Gm. Early physical development was normal, but the patient was retarded mentally, since he did not speak until 3 years of age and toilet habits were established at about this time. An umbilical hernia had been observed since infancy. At about 3 years of age the patient began to deteriorate mentally, lost interest in his surroundings and manifested a speech defect; one year later he was unable to speak, became incontinent of urine and feces and was irritable, noisy and restless. At the age of 5 years, because of abnormal facial features, thyroid was prescribed, with no apparent effect. The blood cholesterol at this time was normal, and an air encephalogram revealed no abnormality.

On admission he appeared as a slightly undersized (height, 120 cm.) idiot (intelligence quotient, 17) boy. His head was enlarged, measuring 59 cm. in circumference and was dolichocephalic and scaphocephalic (fig. 2 *D*). The bones

of the vault showed a thick spongy layer. The sella was not enlarged. The face (fig. 1 *C*) showed a low hair line, prominent orbital ridges, thick eyebrows and depressed root of the nose. Both corneas were clear, and the fundi appeared normal. The neck was short. There was slight lumbar kyphosis. The vertebral bodies of the lumbar and lower thoracic portions of the spine were irregular in outline. The first lumbar and, to a less extent, the second lumbar and the twelfth dorsal vertebrae were smaller than normal and were somewhat wedge shaped and irregular in their anterior aspect (fig. 3 *C*). The thorax was not deformed, but some of the ribs were slightly ribbon shaped. The abdomen protruded; the liver was palpable about 12 cm. below the costal margin, while its upper limits were at the normal level. The spleen could not be felt. There were an umbilical hernia and a repaired inguinal hernia on the left side. The extremities showed no conspicuous changes except for the hands, which were rather short and showed a slightly cone-shaped aspect of the phalanges (fig. 4 *E*).

Neurologic examination revealed only awkward gait and increased deep reflexes. The results of laboratory tests were essentially noncontributory. The electroencephalogram showed diffuse and continuous dysrhythmia, characterized by slow (6 to 7 per second) activity of rather high voltage.

During his stay in the hospital mental deterioration progressed, as shown by a further decrease in the intelligence quotient and an increase in aimless overactivity.

CASE 9.—D. J., a white boy, was admitted to Letchworth Village at the age of 10 years. The paternal side of the family was of Greek and the maternal side of Irish-American extraction, and there was no consanguinity. There was no record of mental defect in the collateral relatives, but none of these persons was examined personally. The family consisted of normal parents and a younger brother, who was physically and mentally normal. An older sib had been stillborn. The patient was born after a normal gestation, with low forceps delivery. He weighed 8 pounds (3,628 Gm.) and showed no physical abnormalities. At 6 months of age it was noted that the child's facial features were somewhat abnormal because of widely spaced eyes and thick, bushy eyebrows.

Mental development was slow, and at 2 years of age the mental defect was obvious but physical development was apparently normal. After 6 years of age he became restless and destructive and showed mental deterioration.

Examination on admission revealed a well developed idiot (intelligence quotient, 20), 153 cm. in height. There was no disproportion in the torso-leg ratio. The head was 52 cm. in circumference and slightly acrocephalic. The bones of the skull were thicker than normal, and the spongy tissue was considerably increased. The face had a peculiar appearance because of a high, somewhat prominent forehead, bushy eyebrows, mild hypertelorism, pug nose and large mouth (fig. 1 *D*). The corneas were clear and the fundi normal. The spine showed considerable rigidity, all movements being limited, especially in its dorsolumbar segment, but there was no scoliosis or kyphosis. The twelfth thoracic vertebra showed the "beaked" appearance described in the cases of complete gargoylism (fig. 3 *D*). There were limitation of extension of the elbow and deformities of the epiphyses of the humerus, radius and ulna. The first phalanges appeared somewhat cone shaped. The ribs were larger than normal. No osseous deformities were noted in the lower extremities. The liver was not enlarged, its inferior limits, as determined roentgenoscopically, being at the level of the costal margin. The spleen was not palpable.

Laboratory examinations gave values within normal limits.

CASE 10.—A. L., a white girl of Italian extraction, was admitted to Letchworth Village at 3 years of age. Information was available concerning three generations on both sides of the family, including 39 members. No other instances of the

disease were observed. No consanguineous marriages had occurred. The patient had a younger brother, who was normal mentally and physically. The patient was born of a normal delivery after an uneventful gestation. The weight at birth was 3,600 Gm. No abnormal features were observed during the first year of life except for a very large tongue, which was "always hanging out." At 3 years of age it was noted that the patient failed to grow in spite of an enormous appetite, and her face had begun to acquire a peculiar aspect. She never acquired any speech or toilet habits and was two years late in walking. At the age of 3 years the intelligence quotient was 26, and no apparent deterioration had occurred over a period of six years.

Examination at the age of 10 years showed a dwarf (height, 98 cm.) girl. The head was large (50 cm. in circumference), the bone of the skull thicker than normal and spongy and the sella elongated in shape. The forehead was low; the hair and eyebrows were abundant; the eyes were set far apart; the root of the nose was depressed; the mouth was prominent with thick, everted lips and a large, thick tongue. The teeth were irregularly spaced and carious. The malar bones were somewhat prominent. The corneas were clear. The neck was short. There was no kyphosis, but the vertebrae showed irregularity in outline and size. Remarkable were the twelfth thoracic vertebra for its small size and the first and second lumbar for their oval form in anteroposterior projection. There was no wedging of vertebrae. The ribs were normal except for the tenth rib, which was spatulated. The abdomen was protruding, and a small umbilical hernia was present. The liver could be palpated 4 inches (10 cm.) below the costal margin and appeared enlarged on roentgenoscopy. The spleen was normal. There was limitation of movement at the elbows, especially on the right side. The hands showed deformity of the three ulnar fingers, limitation of movement and some phalanges were slightly cone-shaped (fig. 4 *F*). The acetabulum and mandular fossa were normal bilaterally.

Laboratory tests showed no abnormalities.

COMMENT

On the basis of the study of these 7 patients and of the cases reported in the literature, one may attempt to outline the diagnostic criteria which are of assistance in the recognition of formes frustes of gargoylism. The clinical diagnosis may present considerable difficulties because of the absence of some characteristic feature usually associated with the disease.

Corneal opacities, a pathognomonic feature of complete gargoylism, was conspicuously absent in all the cases described in this section. It is worth noting that corneas were clear in one third of the cases described in the literature. It is possible that examination with the slit lamp will increase the percentage of corneal lesions observed in cases of incomplete gargoylism, but it is reasonable to assume that lipid infiltration, which is responsible for corneal clouding,[6] may spare the eye while involving other tissues.

6. (*a*) Rochat, G. F.: Die Corneaveränderungen bei der Dysostosis multiplex, Ophthalmologica **103**:353, 1942. (*b*) Berliner, M. L.: Lipin Keratitis of Hurler's Syndrome (Gargoylism or Dysostosis Multiplex), Arch. Ophth. **22**:97 (July) 1939. (*c*) Strauss, L.: The Pathology of Gargoylism, Am. J. Path. **24**:855, 1948.

Enlargement of the liver and spleen was absent in 2 of 7 of the present cases of formes frustes and was not recorded in 22 per cent of the cases described in the literature. Although careful examination may reduce this percentage, the fact remains that the presence of hepatosplenomegaly is not necessary to a diagnosis of gargoylism. Apparently, as shown by pathologic examination, the morbid process may spare occasionally the liver and spleen.

All patients described in this section showed mental defect. However, in the literature there are about 10 cases of incomplete gargoylism with normal mentality. To be sure, in some of these cases psychologic tests were not performed. In 1 of these cases,[7] in which pathologic examination was made, no significant lesions were found in the brain. It would appear, therefore, that in rare instances of gargoylism the pathologic process underlying the disease fails to involve the central nervous system.

Osseous deformities were present in all the cases described here, as well as in all cases reported in the literature, but showed wide variation in extent and character. Dwarfism was present in all but 1 case (case 9) but varied considerably, from the striking degree in case 10 to the almost normal stature in case 8. Deformities of the skull and the peculiar facies were present in varying degrees in all cases described here or in the literature. It should be noted, however, that in the 3 last cases described in this article the face failed to show the striking disfiguration peculiar to complete gargoylism. Whether there exists a facies of gargoylism as characteristic of gargoylism in its clinical variants as is the facies of mongolism, only the examination of a larger number of cases will establish.

Lesions of the vertebrae were present in all cases, but in cases 4 and 10 the changes consisted only of irregularities of shape and contour of the vertebral bodies, whereas in cases 7, 8 and 9 wedge-shaped vertebrae with a hooklike process were observed. In none of these cases, however, was pronounced kyphosis present. Evidence of alterations of bony structure of the extremities was somewhat scanty in all these 7 cases as compared with the findings in complete gargoylism, but the difference was one of degree rather than of nature. The fact should be stressed, in conclusion, that deformities of bone may be of such mild degree as to escape detection unless careful roentgenologic examination is made of the skeletal system. Undoubtedly, many instances of formes frustes remain undiagnosed for lack of such an examination.

The diagnosis in the present cases was based on association of mental deficiency and characteristic deformities of bone, including those of the skull, face and spine. In 5 cases enlargement of the liver added evidence in favor of gargoylism. It is reasonable to assume that other formes

7. Strauss, R.; Merliss, R., and Reiser, R.: Gargoylism: Review of Literature and Report of the Sixth Autopsied Case with Chemical Studies, Am. J. Clin. Path. **17**:671, 1947.

frustes do occur showing even fewer clinical manifestations than those here reported. The association of a gargoyle-like face and severe mental defect without other manifestations of the disease was personally observed on several occasions, but no pathologic evidence has thus far been obtained to corroborate the diagnosis of gargoylism. Strauss and associates [7] described a forme fruste in which the lesions were mainly in the bones and the liver, without involvement of the brain. Similar cases were described by de Lange and associates.[8]

The present concept of this aspect of the disease is of necessity somewhat elastic and conjectural until new pathologic data are available. It is, in fact, on the pathologic picture that the diagnosis of gargoylism in its clinical varieties is ultimately based.

Differential diagnosis of the formes frustes of gargoylism and sporadic cretinism may offer difficulty. In fact, cases 6, 7 and 8 were considered instances of cretinism, and the condition was treated accordingly for many years. Several similar instances may be found in the literature. Mental and physical retardation, dwarfism, certain facial traits, plump hands and "pot belly" are traits common to the two conditions. However, the type of bony deformities, lack of retardation in ossification, absence of myxedema and the hypertrichosis are useful criteria in differentiating gargoylism from cretinism when both corneal clouding and hepatosplenomegaly are absent. Moreover, as was pointed out by Hässler,[9] values for blood calcium and cholesterol are normal in gargoylism and increased in cretinism.

The differentiation from Morquio's disease (eccentro-osteochondrodysplasia) may be difficult. Dwarfism, hypertelorism, saddle nose, short neck, kyphosis and osseous deformities are conspicuous in both conditions. It has been pointed out [10] that the head is not enlarged in Morquio's disease, the ribs are small, deformities of the chest are conspicuous, the beaked deformation of the vertebrae is lacking and there is no limitation of movements of joints but, rather, laxity of joint ligaments. Moreover, mental defect, hepatosplenomegaly and corneal opacities are absent in Morquio's disease. These criteria may be valid in single cases, but one cannot escape the conclusion that the two conditions are very similar, if not identical (Ruggles,[11] de Rudder [12]).

8. de Lange, C.; Gerlings, P. G.; de Kleyn, A., and Lettinga, T. W.: Some Remarks on Gargoylism, Acta pædiat. **31**:398, 1944.

9. Hässler, E.: Die Beziehungen der Hurlerschen Krankheit zum Kretinismus, Monatsschr. f. Kinderh. **86**:96, 1941.

10. Zellweger, H., and Schaichet, M.: Zwei Fälle von Dysostosis Morquio, Helvet. pædiat. acta **3**:208, 1948.

11. Ruggles, H. E.: Dwarfism Due to Disordered Epiphyseal Development, Am. J. Roentgenol. **25**:91, 1931.

12. de Rudder, B.: Ueber Phosphatiddiathese und ihr Verhältnis zu Dysostosis multiplex and Dysostosis Morquio, Ztschr. f. Kinderh. **63**:407, 1943.

PATHOLOGY OF GARGOYLISM

Since the recognition of gargoylism is based mainly on pathologic changes, it is pertinent to report the pathologic picture in 2 incomplete cases described in the preceding section (cases 4 and 6).[12a]

CASE 4.—Gross significant changes were observed in the brain, the liver and the spleen. The brain was reduced in weight (1,050 Gm.) and showed mild internal hydrocephalus involving uniformly all portions of the ventricular system. The main cortical patterns were not altered, but slight atrophy of the convolutions was present. The cerebral matter exhibited a peculiar rubbery consistency. The cerebellum, pons, medulla and spinal cord appeared grossly normal.

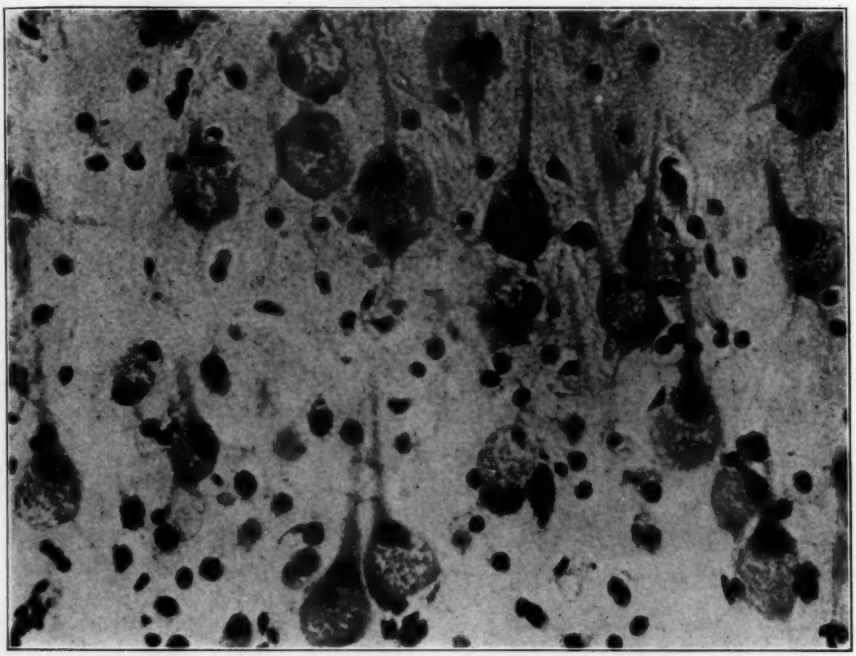

Fig. 5 (case 4).—Pyramidal cells of the cerebral cortex, showing distention of the cellular body, displacement of the nucleus, disappearance of Nissl bodies and granular material in the cytoplasm. Nissl stain.

The liver weighed 1,890 Gm., or was over twice its normal weight, and showed a peculiar hard consistency and grayish color. No derangement of connective tissue was grossly apparent throughout the organ. The spleen was likewise enlarged, being about five times its normal size. It weighed 500 Gm. and showed the same peculiar hard, dry, grayish aspect as the liver.

Histologic examination of the nervous system showed striking changes in the nerve cells (fig. 5). In preparations stained with the Nissl method the body of the

12a. After this paper was submitted for publication, an autopsy was performed in case 8. The observations were essentially the same as those in case 4.

cells was swollen and distorted. The cytoplasm contained small vacuoles and few, if any, Nissl bodies. The nucleus was displaced toward the periphery, showing often degenerative changes. Bielschowsky and Bodian methods brought out distinctly the swelling and distortion of the cells and showed, in addition, that the neurofibrils had disappeared. With these methods, varying amounts of granular material, which apparently had escaped the action of the solvents employed, could be observed within the cytoplasm. It was, however, with specific methods for lipid material in frozen sections that a large amount of granular material was observed to fill the swollen cytoplasm. The material stained very poorly with scarlet red, sudan III,

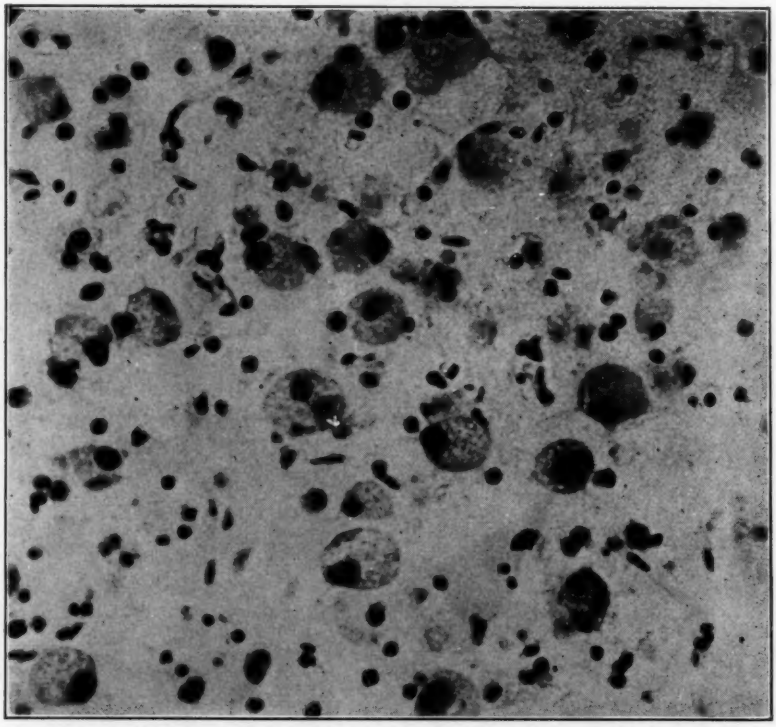

Fig. 6 (case 4).—Neurocellular lesions in the basal ganglia, similar to those in figure 5. Nissl stain.

nile blue and osmic acid. It gave a positive reaction with Schiff's reagent in sections treated with periodic acid according to McManus' directions,[13] and it stained well with thionine according to Feyrter's method.[14] The solubility tests performed by

13. McManus, J. F. A.: The Periodic Acid Routine Applied to the Kidney, Am. J. Path. **24**:643, 1948.

14. Feyrter, F.: Ueber ein sehr einfaches Verfahren der Markscheidenfärbung, zugleich eine neue Art der Färberei, Virchows Arch. f. path. Anat. **296**:645, 1936.

Feyrter's method on frozen sections which had been placed ten to fifteen minutes in the solvent showed that the lipid material was insoluble in cold acetone, partially soluble in ether or alcohol, soluble in hot chloroform and methyl alcohol and somewhat soluble in hot acetone.

Various stages of this characteristic neurocellular alteration could be observed, from extreme distention of the cytoplasm and disappearance of the nucleus to a few granules located in the corner of a slightly enlarged cell. Whatever the stage, no region of the central nervous system was spared, and even the neuron cells of the plexuses showed a similar change.

With the Cajal method, the macroglia showed often moderate hyperplastic changes, and some cells were larger than normal. Stains with Feyrter's method

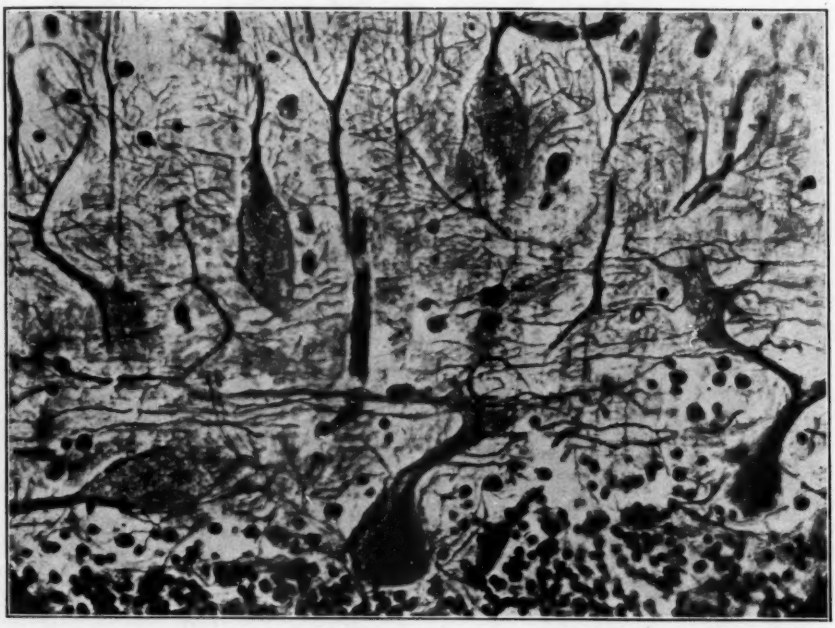

Fig. 7 (case 4).—Characteristic fusiform swellings of the dendrites of Purkinje cells, containing granular material. DaFano stain.

revealed lipid material in the microglia, although it was difficult to differentiate a small swollen nerve cell with pyknotic nucleus from a distended glia cell in these preparations. Altogether, the changes in the macroglia were minimal as compared with the neurocellular lesions. Microglia and oligodendroglia were apparently inactive. The blood vessels showed no alteration, and no lipid infiltration was seen in the vascular walls.

In the cerebral cortex (fig. 5) most of the nerve cells were involved, but wide variations were observed in the degree of the process within the same region. Considerable dropping out of nerve cells was observed, resulting in cytoarchitectural derangement. There was no selective laminar involvement throughout the cortex,

although the swelling of the large pyramidal cells stood out more conspicuously because of the size of the cell. There was, likewise, no selective involvement of any particular cortical field.

In the white matter of the hemisphere, no significant changes were seen. The myelin and axis-cylinders appeared normal. Occasionally, perivascular collections of compound granular elements loaded with fatty material were observed. This material, however, stained brilliant red with scarlet red and dissolved promptly in

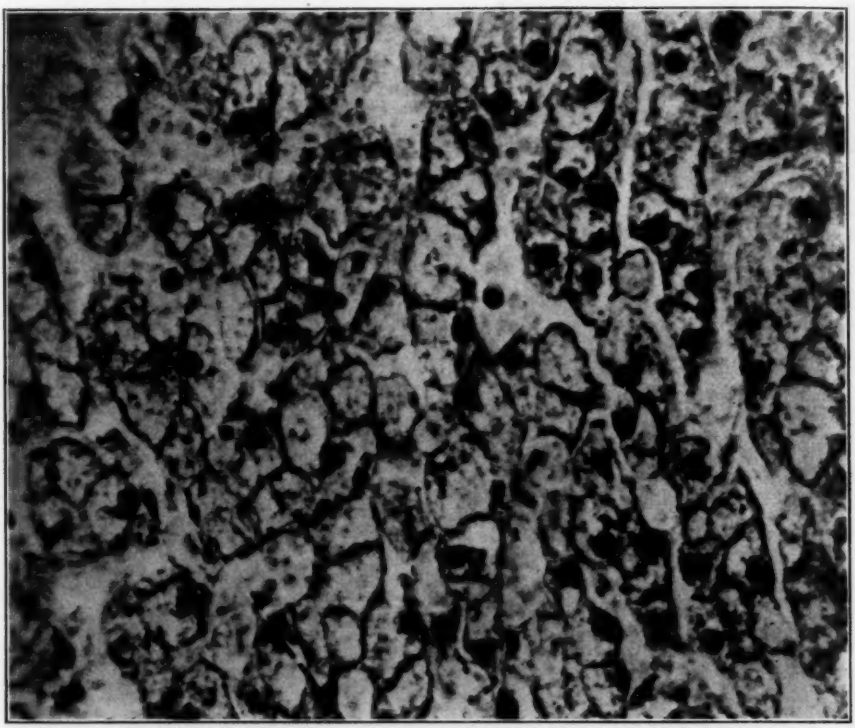

Fig. 8 (case 4).—Liver cells, showing swelling and vacuolation. Hematoxylin and eosin stain.

all fat solvents. It was obviously of a different nature from the lipid content of the nerve cells.

The basal ganglia and thalamic nuclei were involved in a manner similar to that of the cortex (fig. 6). The large nerve cells were conspicuous by their marked swellings and advanced nuclear alteration. No abnormal deposits of iron, calcium or pigments were observed in preparations stained by suitable methods.

Throughout the midbrain, medulla and spinal cord a similar picture of neurocellular swelling and lipid infiltration was noted, but loss of neuron cells was slight as compared with that in the cortical regions. Some formations, such as the motor

nuclei of the medulla and the anterior horn of the spinal cord, were more involved than others, such as the inferior olivary nuclei or the substantia nigra. In the cerebellum, the Purkinje cells were decreased in number, and the remaining ones were often swollen and of bizarre shape. A striking alteration was observed in the molecular layer, consisting of peculiar fusiform swellings of dendrites of the Purkinje cells containing large amounts of lipid material similar in staining properties to the lipid content of the nerve cells (fig. 7). The granular layer and the white matter of the cerebellum showed no alterations.

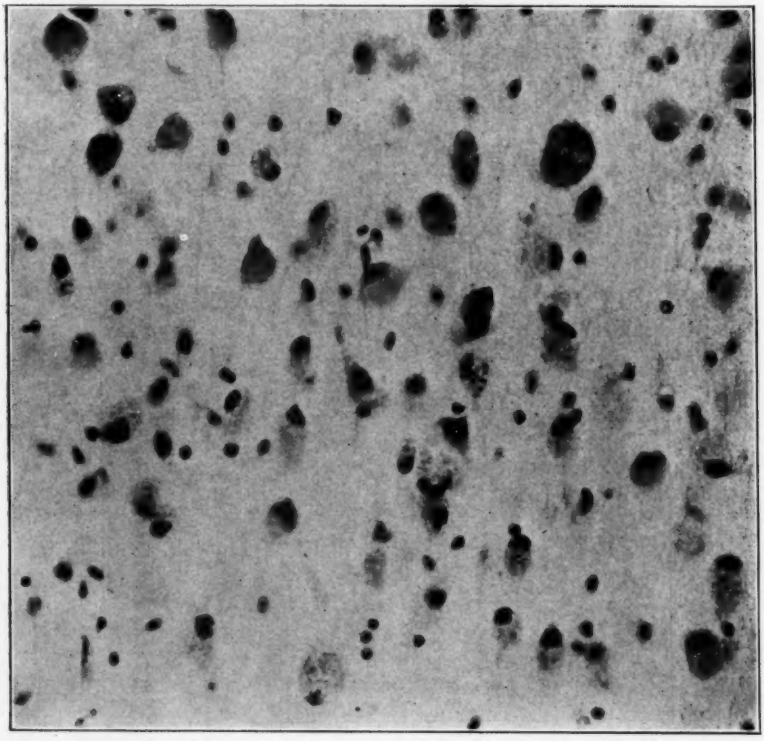

Fig. 9 (case 6).—Neurocellular lesions in the cerebral cortex, similar to those in figure 5. Nissl stain.

Histologic examination of the liver revealed changes in the hepatic cells, whereas no increase of connective tissue was apparent. Almost all the cells of the liver were enlarged, being twice or more their normal size; the cytoplasm was grossly vacuolated, and the nuclus was displaced toward the periphery (fig. 8). In frozen sections stained by suitable methods, the vacuoles were seen to contain lipid material similar in staining and solubility properties to that found in the central nervous system. The Kupffer cells were not proliferated but were somewhat swollen and apparently contained lipids.

The spleen showed no conspicuous alteration of lymphatic tissue, but the reticulum cells were larger than normal and contained lipid material which possessed the staining properties of the lipid in the liver. There was congestion throughout the organ but no significant vascular alterations.

Examination of cartilage from the ribs and sternum showed no lipid deposit in the cartilage corpuscles. These appeared normal in every respect. Osseous tissue was not studied. Examination of the bone marrow obtained from the sternum

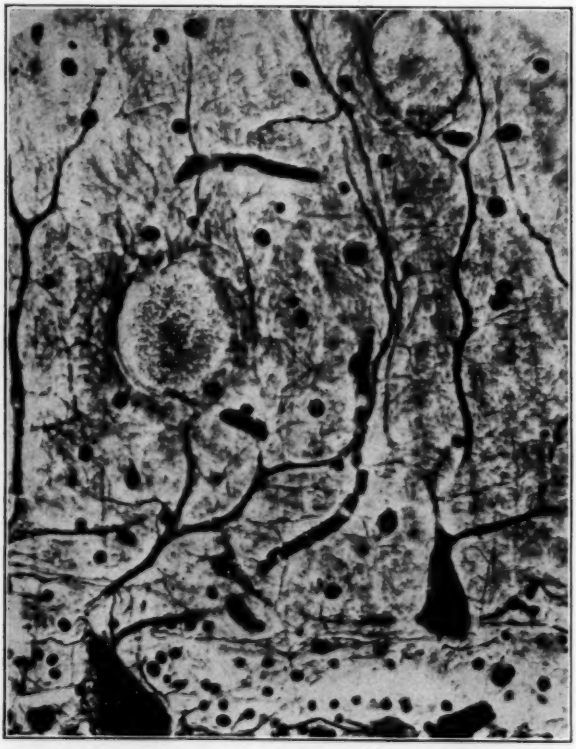

Fig. 10 (case 6).—Characteristic globoid swellings in the molecular layer of the cerebellum. Braunmühl stain.

showed nothing abnormal. Histologic examination of other organs and tissues revealed no significant changes.

Case 6.—Grossly, the thoracic and abdominal viscera exhibited no significant changes. The liver weighed 1,200 Gm. and the spleen 180 Gm., and neither organ showed gross evidence of lipid deposits.

The brain weighed 980 Gm. It appeared atrophic, the convolutions being shrunken and the sulci gaping throughout. The volume of the white matter was notably reduced, and the ventricles were dilated. The cerebellum, pons, medulla and spinal cord appeared grossly normal.

Histologic examination of the central nervous system showed changes in the nerve cells similar to those encountered in case 4 (fig. 9). Cytoplasmic swellings and lipid infiltrations were present throughout the central nervous system and in the nerve cells of the peripheral ganglia. The cerebral cortex was unevenly involved, the occipital regions showing less pronounced alterations than the other cortical regions. The basal ganglia, thalamus and midbrain were extensively involved, most of the cells presenting advanced swellings. The cerebellum showed lesions identical with those described in case 4. Striking were the swelling of the dendrites of many Purkinje cells (fig. 10). The solubility and staining properties of the infiltrating lipids were similar to those reported in case 4. The neuroglial reaction in the cortical field was more active than that in the previous case. Numerous hypertrophic astrocytes were observed in the deep cortical layer and in the subcortical white matter.

The myelin sheaths in the centrum ovale were reduced in number, were thinner than normal and stained palely with hematoxylin. Glial elements were apparently increased in number, probably because of the reduction of myelin and the consequent crowding of glial nuclei. A striking lesion in the white matter, consisting of large areas of active demyelination, was found repeatedly. In these areas large amounts of lipid material were observed either free in the tissue or collected within scavenging cells. This material showed properties entirely different from those of the lipid infiltrating the nerve cells. It stained red with scarlet red, black with osmic acid and dissolved readily in xylene, acetone and ether. Considerable quantities of this lipid were found in perivascular spaces within the area of demyelination.

The liver was not enlarged and was of normal weight. However, histologic examination showed alterations similar to those in the preceding case, although much less advanced. The vacuoles were smaller and the nuclear alterations mild. The spleen was not enlarged and was normal histologically. The lungs, heart and kidneys did not show vacuolated cells in the available preparations. The pituitary gland was normal. The thyroid appeared well developed and weighed 34 Gm. Histologically, there was considerable irregularity in the size of follicles, but the epithelium appeared normal. Cartilage from the ribs showed no histologic abnormalities. The bones were not examined histologically.

COMMENT

Although only a few pathologic descriptions can be found in the literature, there is general agreement concerning the essential lesion of the central nervous system in typical gargoylism. This consists essentially of ubiquitous swelling of the nerve cells with cytoplasmic deposit of a granular material. The intensity and distribution of this characteristic lesion vary from case to case, and minor histologic deviations in glial reaction and destruction of myelin are occasionally observed. Thus, in Tuthill's [15] description of one of the original Hurler [16] cases the unusual features were overgrowth of vascular adventitia and diffuse thinning of

15. Tuthill, C. R.: Juvenile Amaurotic Idiocy: Marked Adventitial Growth Associated with Skeletal Malformations and Tuberculomas, Arch. Neurol. & Psychiat. **32**:198 (July) 1934.

16. Hurler, G.: Ueber einen Typ multipler Abartungen, vorwiegend am Skelettsystem, Ztschr. f. Kinderh. **24**:220, 1919.

the white matter of the hemispheres. In the case of Ashby and associates,[17] which was clinically described by Jewesbury and Spence,[18] masses of extracellular lipid material were observed throughout the nerve tissue. The cases described by Kressler and Aegerter,[19] de Lange,[20] Kny [21] and Green [22] and cases 3, 4, 5, 6 and 7 of Lindsay and associates [23] conform essentially to the characteristic pathologic picture of the central nervous system.

The pathologic changes in cases of formes frustes have been reported by de Lange and associates[8] and Strauss and associates.[7] No extensive fatty infiltration of the nervous system was observed in their cases. However, in an atypical case previously described [24] and in the present 2 cases of formes frustes lesions of the central nervous system were observed entirely similar to those described in the complete forms of the disease.

Unlike the lesions of the central nervous system, the alterations in other organs vary considerably from case to case, even in typical instances of gargoylism. In fact, no viscera other than the brain were involved in the cases of Tuthill [15] and Ashby and associates.[17] In the cases described by Kny [21] and de Lange [20] infiltration only of the liver and the brain was noted. Kressler and Aegerter [19] found lipids in the liver, spleen and pituitary body, whereas in Green's [22] case large vacuolated cells were observed in the heart, aorta, kidney, intestinal wall and pancreas, in addition to the infiltration of the liver and spleen. Likewise, Lindsay and associates [23] noted more widespread lesions than those usually described by other investigators. In their several cases, various types of cells were altered, namely, reticuloendothelial cells, both fixed and wandering; connective elements, including fibrocytes, chondrocytes and astrocytes and the parenchyma cells of the liver, spleen, pituitary gland and

17. Ashby, W. R.; Stewart, R. M., and Watkin, J. H.: Chondro-Osteo-Dystrophy of the Hurler Type (Gargoylism): A Pathological Study, Brain **60**:149, 1937.

18. Jewesbury, R. C., and Spence, J. C.: Two Cases: Oxycephaly and Acrocephaly with Other Congenital Deformities, Proc. Roy. Soc. Med. **14**:30, 1935.

19. Kressler, R. J., and Aegerter, E. E.: Hurler's Syndrome (Gargoylism), J. Pediat. **12**:579, 1938.

20. de Lange, C.: Pathologic Anatomy of Gargoylism, Psychiat. en neurol. bl. **46**:2, 1942.

21. Kny, W.: Zur Kenntnis der Dysostosis multiplex Typ Pfaundler-Hunter, Ztschr. f. Kinderh. **63**:366, 1942.

22. Green, M.: Gargoylism (Lipochondrodystrophy), J. Neuropath. & Exper. Neurol. **7**:399, 1948.

23. Lindsay, R.; Reilly, W. A.; Gotham, T. S., and Skahen, R.: Gargoylism: Study of Pathologic Lesions and Clinical Review of Twelve Cases, Am. J. Dis. Child. **76**:239 (Sept.) 1948.

24. Jervis, G. A.: Familial Mental Deficiency Akin to Amaurotic Idiocy and Gargoylism, Arch. Neurol. & Psychiat. **47**:943 (June) 1942.

thyroid. Of the present 2 cases, both of formes frustes, there was conspicuous involvement of the liver and spleen in 1 case and histologic evidence of changes in the liver in the other. It is clear, therefore, that in the extent and distribution of pathologic lesions wide variations occur, which are not unlike those encountered in the clinical picture.

A controversial point of considerable importance is the nature of the pathologic lesions of bone and cartilage tissue. Schmidt,[24a] Washington [25] and Lindsay and associates [23] noted swelling, vacuolation and infiltration with abnormal material of osteoblasts and chondrocytes and interpreted the osseous lesions as due to abnormal function of these cellular elements. Others [26] were unable to confirm these observations and stated the belief that the skeletal lesion was not directly due to abnormal storage. In the present cases, examination was limited to the cartilage of the ribs, but no swelling or infiltration of cells was found. Obviously, examination in a larger number of cases is necessary to solve this problem.

There seems to be little doubt that gargoylism is a disease of abnormal storage, but the nature of the material stored in the cells is still undetermined. It has recently been claimed by Lindsay and associates [23] that the intracellular material is a polysaccharide, presumably glycogen, the evidence being based on the results of biopsy. Specimens of cartilage and liver from 2 patients gave a positive reaction for glycogen with the Best carmine stain and in the Feulgen-Bauer test. The same methods applied to autopsy material gave negative results, presumably because of postmortem glycolysis. No glycogen could be demonstrated in the present 2 cases, but the material had stood several hours before fixation in alcohol, so that postmortem glycolysis had certainly occurred. It should be noted, however, that the intracellular material withstood prolonged action of solution of formaldehyde U. S. P., in which glycogen is readily soluble, and it was extracted by chloroform and methyl alcohol, which are lipid solvents. Moreover, in the present cases the intracellular material was stained by Feyrter's method, which brings out complex lipid and lipoproteins.

If the available evidence indicates that the infiltrating material is a lipid, its exact chemical constitution is still unknown. Disagreement exists among investigators concerning its staining and solubility properties.

24a. Schmidt, M. B.: Die anatomischen Veränderungen des Skelets bei der Hurlerschen Krankheit, Zentralbl. f. allg. Path. u. path. Anat. **79**:113, 1942.

25. Washington, J. A.: Lipochondrodystrophy, in Brennemann, J. Practice of Pediatrics, Hagerstown, Md., W. F. Prior, Inc., 1945, vol. 4, chap. 30.

26. (*a*) Zierl, F.: Ueber Skeletveränderungen bei der juvenilen Form der amaurotischen Idiotie, Ztschr. f. d. ges. Neurol. u. Psychiat. **131**:400, 1930. (*b*) Binswanger, E., and Ullrich, O.: Ueber die Dystostosis multiplex (Typus Hurler) und ihre Beziehungen zu andere Konstitutionsanomalien, Ztschr. f. Kinderh. **54**:699, 1933. (*c*) Kressler and Aegerter.[19] (*d*) Strauss, Merliss and Reiser.[7] (*e*) Kny.[21] (*f*) Green.[22]

For instance, positive staining with scarlet red has been reported by Tuthill,[15] Ashby and associates,[17] Kny [21] and Green [22] and almost negative results by Kressler and Aegerter,[19] de Lange [20] and Lindsay and associates [23] and in the present cases. It is possible that these discrepancies are due to variations in the technics used or to differences in the metabolic stages of the lipid involved. To be sure, only chemical methods of analysis will offer conclusive data. Preliminary analyses in the cases here described show the lipid material to contain nitrogen, phosphorus and a sugar. It differs therefore, from the lipid involved in Niemann-Pick disease (sphingomyelin), in Tay-Sachs disease, or infantile amaurotic familial idiocy (ganglioside) or in Gaucher's disease (kerasin). It is not clear yet whether this lipid differs from the lipid present in juvenile amaurotic familial idiocy, a condition almost identical with gargoylism from the neuropathologic aspect.

It has been pointed out by Ashby and associates [17] that gargoylism can be considered a lipidosis, and successive observations showing widespread infiltration of organs have confirmed this point of view. It should be noted, however, that in the present cases, as well as in the majority of previously reported cases, the parenchyma cells of the brain and liver were much more involved than other elements, while the reticuloendothelial cells represented in the brain by the microglia and in the liver by the Kupffer cells appear relatively spared (the latter) or completely inactive (the former). This finding is contrary to the picture seen in the commoner forms of generalized lipidosis and confers a distinctive character of localized lipidosis to gargoylism.

ETIOLOGY OF GARGOYLISM

The histories of cases of complete and of atypical gargoylism here reported, as well as those found in the literature, show a conspicuous lack of evidence in favor of environmental factors as the cause of the disease. Trauma at birth, disease or old age of the mother, postnatal conditions and other factors which are usually considered significant in detecting the influence of environmental agencies are not apparent in any consistent way. On the other hand, it is clear that the condition runs in families. When both complete and atypical forms are considered, of 85 families available for study, 26 had two or more members affected. If the families with only one sib are excluded, 37.6 per cent had two or more affected sibs, and 52 per cent of the cases showed familial incidence. These high figures, together with the absence of any demonstrable common factor in the environment, indicates the possibility of genetic mechanisms.

Since all parents of affected persons show no evidence of the disease, the most likely genetic hypothesis is that of monomeric recessivity. On this hypothesis, the expected ratio of affected to normal children in the

sibship is 1 : 3 (25 per cent). It may be seen from the data presented in the appended table that the crude ratio is higher (1 : 1.2, or 45 per cent). It is well known, however, that such high percentages occur with human recessive traits. Corrections of raw percentages by several special methods of statistical analysis have been devised. In table 1, the data collected in the appendix are arranged according to Bernstein's a priori method.[27]

In this table, s is the size of the sibship; n, the number of sibships; x, the expected number of affected sibs on the basis of the hypothesis of recessivity; t, the observed number of affected sibs, and m^2, the quadratic error; x is $\frac{sp}{1-q^s}$ and m^2 is x_s (q—xsq^s), p being 0.25 and q= (1—p). It may be seen that the difference between expectation

TABLE 1.—*Presentation of Data in Appendix According to Bernstein's Statistical Method*[27]

s	ns	xs	xns	ts	m^2	m^2ns
1	15	1.000	15.000	15	0.000	0.000
2	26	1.143	29.718	32	0.122	3.172
3	18	2.297	23.346	26	0.263	4.734
4	11	1.463	16.093	15	0.420	4.620
5	3	1.639	4.917	3	0.592	1.776
6	4	1.825	7.300	7	0.776	3.104
7	3	2.020	6.060	10	0.970	2.910
8	2	2.223	4.446	4	1.172	2.344
9	1	2.433	2.433	6	1.380	1.380
11	1	2.870	2.870	4	1.805	1.805
Total	84	.....	112.183	122	.....	25.835

and observation is 9.8, or slightly less than twice the standard error, 5.09. The agreement is statistically significant.

A better agreement may be obtained with Lenz's method of corrected percentage.[28] As seen in table 2, the difference between the expected and the observed percentage is 1.68, or less than the standard error, 2.73. The significances of s, n, t, p and q are the same as in table 1. The quadratic error is $P\ \frac{100-P}{S}$, where P is the percentage and S the sum of sibs.

The data, therefore, are consistent with the theoretic expectation of recessivity with respect to the ratio of affected to normal members in the sibship.

A second basic requirement for rare recessive genes is that the rate of consanguinity among parents of affected members be above the rate observed in the general population. A high incidence of cousin mar-

27. Bernstein, F.: Variationen und Erblichkeitstatistik, in Baur, E., and Hartmann, M.: Handbuch der Vererbungswissenschaft, Berlin, 1929.

28. Lenz, F.: Methoden der menschlichen Erblichkeitforschung, in Gottschlich: Handbuch der hygienischen Untersuchungsmethoden, Jena, 1929.

riages in the families of patients is, in fact, a valuable criterion for the detection of rare recessive genes (Dahlberg [29]). In the present material the parents were cousins in 11 families out of 103. In 52 families, however, the information was not complete, so that the figure 11 per cent is presumably low. If the incidence of cousin marriages in the general population is estimated as between 0.5 and 1 per cent, it is apparent that the discrepancy is significant, the incidence of consanguinity in families with gargoylism being at least ten times the incidence in the general population. Using Hogben's [30] formulas, a 10 per cent incidence of cousin marriages is expected of a recessive gene having a frequency in the general population of 1:40,000, which may well be the frequency of gargoylism.

TABLE 2.—*Data Presented According to Lenz's Method of Corrected Percentages*

s	ns	$\frac{1}{1-q^s}$	$\frac{s}{1-q^s}$	ts	%	m^2
1	15	4.000	60.0000	15	25.000	.....
2	26	2.2867	118.8564	32	26.932	.....
3	18	1.7297	93.9438	26	27.675	.....
4	11	1.4629	64.3676	15	23.303	.....
5	3	1.3116	19.6740	3	15.248	.....
6	4	1.2165	29.1960	7	23.975	.....
7	3	1.5440	32.4240	10	30.841	.....
8	2	1.1113	17.7808	4	22.502	.....
9	1	1.0612	9.7308	6	61.659	.....
11	1	1.0400	11.4400	4	34.965	.....
Total	..	.....	457.2134	122	26.683	7.495

The extreme rarity of the occurrence of cases of gargoylism among aunts, uncles or cousins of affected persons fits well with the theoretic expectation in the case of recessive traits with a frequency of the order of magnitude assumed for gargoylism.

In conclusion, all data are consistent with the quantitative requirement of monomeric recessivity and make it probable, as indicated already by others [31] on the basis of a more limited number of cases, that gargoylism is determined by a single autosomal recessive gene.

29. Dahlberg, G.: Genetics of Human Population, Advances in Genetics **2**:67, 1948.

30. Hogben, L. T.: An Introduction to Mathematical Genetics, New York, W. W. Norton & Company, 1946.

31. (*a*) Scharf, J.: Ein Beitrag zur Kenntnis der Dysostosis multiplex unter besonderer Berücksichtigung der Erbverhältnisse, Arch. f. Augenh. **143**:477, 1941. (*b*) Böcker, E.: Zur Erblichkeit der Dysostosis multiplex, Ztschr. f. Kinderh. **63**:407, 1942. (*c*) Halperin, S. L., and Curtis, G. M.: The Genetics of Gargoylism, Am. J. Ment. Deficiency **46**:298, 1942. (*d*) Wolff, J.: Ueber das Syndrom von Pfaundler-Hurler, Ztschr. f. menschl. Vererb.-u. Konstitutionslehre **27**:682, 1944.

An identical genetic behavior is found for other types of mental deficiency, e. g., for amaurotic idiocy [32] and for phenylpyruvic idiocy,[33] in which, as in gargoylism, the available evidence indicates that a metabolic error is associated with the mental defect. Many data have accumulated during the past few years indicating that genes control biochemical reaction,[34] and examples of single biochemical reactions, the absence of which is due to substitution of a single recessive gene, are numerous. It is not surprising, therefore, that gargoylism, a condition determined by, or coexistent with, a metabolic abnormality, is found to be genetically conditioned by a recessive gene.

SUMMARY

A study of 10 cases of gargoylism is presented with the purpose of showing the importance of the formes frustes of the disease.

In the first part, 3 cases showing the complete clinical picture of gargoylism are reported, and the characteristic clinical features of the disease are reviewed.

In the second part, 7 cases are described showing some characteristic features of gargoylism but lacking others. Diagnostic criteria which may help in the recognition of these formes frustes are outlined, and the relation of incomplete, atypical variants to the complete forms of the disease is discussed.

In the third part, the pathologic findings in 2 cases of formes frustes of gargoylism are described. The lesions of the brain in these cases were similar to those found in the complete form of the disease, thus indicating a common underlying pathologic process. The nature of this process is briefly commented on.

In the fourth part, the etiologic aspects of gargoylism are discussed. On the basis of the data collected in the appendix, it is shown that the disease, in its typical and incomplete forms, is genetically determined. Its rate of incidence in families and the high percentage of cousin marriages among parents of affected persons are consistent with the hypothesis that the condition is determined by a single recessive gene.

APPENDIX

In table 3, all cases of gargoylism available in the medical literature have been tabulated.

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32. Hogben.[30] Sjögren, T.: Die juvenile amaurotische Idiotie, Hereditas **14**:197, 1931. Slome, D.: The Genetic Basis of Amaurotic Family Idiocy, J. Genetics **27**:363, 1934.

33. Jervis, G. A.: The Genetics of Phenylpyruvic Oligophrenia, J. Ment. Sc. **85**:719, 1939.

34. Bonner, D. M.: Genes as Determiners of Cellular Biochemistry, Science **108**:735, 1948.

TABLE 3.—*Family and Clinical Data in Cases of Gargoylism Reported in the Literature*

Author	Sex	Age	Sibs N	Sibs A	Consanguinity	Mental Defect	Dwarf	Bone Changes: Skull	Face	Spine	Limbs	Hepatosplenomegaly	Corneal Clouding
Hunter, C.: Proc. Roy. Soc. Med. **10**: 104, 1916..	M	10	?	2	+	+	+	+	+	—	+	+	—
	M	8				+	+	+	+	—	+	+	—
Hurler [10]	M	4	4	1	?	+	+	+	+	+	+	+	+
	M	2	0	1	?	+	+	+	+	+	—	—	+
Jewesbury and Spence [18]	M	5	1	1	?	+	+	+	+	?	+	—	+
Thoenes, F.: Jahrb. f. Kinderh. **110**: 167, 1925..	M	10	2	1	?	±	+	+	+	+	+	+	—
Putnam, M. C., and Pelkan, K. F.: Am. J. Dis. Child. **29**: 51 (Jan.) 1925	F	2	3	1	?	+	—	+	+	+	+	+	+
Nonne, M.: Deutsche Ztschr. f. Nervenh. **83**: 263, 1924	F	16	3	3	?	—	+	+	+	+	+	?	—
	F	16				—	+	+	+	+	+	?	—
	F	9				—	+	+	+	+	+	?	—
Heimholz, H. J., and Harrington, E. R.: Am. J. Dis. Child. **41**: 998 (April) 1931	M	4	0	2	?	+	+	+	+	+	+	—	+
	F	2				+	?	+	+	+	+	—	+
Ruggles [11]	F	13	4	3	?	+	+	+	+	+	+	?	+
	M	8				+	+	+	+	+	+	?	+
	?	?				?	?	?	?	?	?	?	—
Zierl [26a]	M	21	4	3	?	+	+	+	+	?	+	—	—
Binswanger and Ullrich [26b]	M	7	1	1	+	+	+	+	+	+	+	—	+
	M	1	1	1	—	+	—	+	+	+	+	—	+
Davis, D. B., and Currier, F. P.: J. A. M. A. **102**: 2173 (June 30) 1934	M	9	1	2?	?	?	?	+	+	—	+	+	—
	M	6				?	?	+	+	—	+	+	—
Jansen, M.: Ztschr. f. Orthop. Chir. **61**: 253, 1934.	M	4	?	?	?	+	+	+	+	+	+	?	?
Reilly, W. A.: Endocrinology **19**: 639, 1935....	M	6	?	?	?	+	+	+	+	+	+	+	—
	M	2				+	+	+	+	—	+	+	+
Ellis, R. W. B., and others: Quart. J. Med. **29**: 119, 1936	F	18	2	2	—	+	+	+	+	+	+	+	+
	F	5	2	1	—	+	+	+	+	+	+	+	+
	F	4	0	1	—	+	+	+	+	+	+	+	+
	M	3	2	1	?	+	—	+	+	+	+	+	+
	M	1	4	1	?	+	?	+	+	+	?	+	+
	M	1	?	?	?	+	?	+	+	+	—	+	+
	M	1	0	1	?	+	—	+	+	+	—	—	+
de Lange, C., and Woltring, L.: Acta pædiat. **19**: 71, 1936	M	5	1	2	—	+	—	+	+	—	—	+	—
	M	14				+	+	+	+	—	+	+	—
Cockayne, E. A.: Proc. Roy. Soc. Med. **30**: 104, 1936	M	9	1	1	—	+	—	+	+	+	+	+	—
	M	4	1	1	—	+	—	+	+	—	+	+	—
Müller, R. W.: Fortschr. a. d. Geb. d. Röntgenstrahlen **53**: 877, 1936	M	7	?	?	?	+	+	+	+	?	+	?	?
	M	3	?	?	?	+	+	+	+	+	+	?	?
Liebenam [4]	M	13	3	1	—	±	+	+	+	+	+	+	+
Ten Bokkel Huinink, A.: Maandschr. v. kindergeneesk. **6**: 449, 1937	M	5	7	1	?	+	?	+	+	?	+	+	+
Nordmann, J.: Bull. Soc. d'opht. de Paris **49**: 256, 1937	M	6	1	2	?	+	+	+	+	+	+	+	+
	F	2				+	+	+	+	+	+	+	+

Author	Sex	Age	Sibs N	Sibs A	Consanguinity	Mental Defect	Dwarf	Bone Changes: Skull	Face	Spine	Limbs	Hepatosplenomegaly	Corneal Clouding
Nordmann, J.: Bull. Soc. d'opht. de Paris **49**: 256, 1937	M	6	1	2	?	+	+	+	+	?	+	+	+
	F	3				+	+	+	+	+	+	+	+
Bouman, H. D.: Nederl. tijdschr. v. geneesk. **81**: 3001, 1937	?	?	?	?	?	—	—	±	±	+	?	?	+
Tombleson, J. B. L.: Proc. Roy. Soc. Med. **30**: 1070, 1937	M	3	4	1	—	+	+	+	+	+	+	?	+
Kressler and Aegerter [19]	M	6	5	1	?	+	+	+	+	+	+	+	+
Besdziek, F.: Monatschr. f. Kinderh. **76**: 305, 1938	M	5	?	?	—	+	?	+	+	+	+	—	+
	M	4				+	?	+	+	+	+	—	+
Ellis, R. W. B.: Proc. Roy. Soc. Med. **31**: 770, 1938	F	2	?	?	—	+	+	+	+	+	+	+	+
Bindschedler, J. J., and others: Rev. franç. de pédiat. **14**: 116, 1938	M	8	1	2	?	+	+	+	+	+	+	+	+
	F	5				+	+	+	+	+	+	+	+
Slot, G., and Burgess, G. L.: Proc. Roy. Soc. Med. **31**: 1113, 1938	F	6	0	1	?	?	—	+	+	—	+	+	+
Schmidt, R.: Klin. Monatsbl. f. Augenh. **100**: 616, 1938	M	47	7	4	+	?	+	+	+	?	+	?	+
	F	45				+	+	+	+	?	+	?	+
Engel, D.: Arch. Dis. Childhood **14**: 217, 1939	M	12	4	2	—	+	+	+	+	—	+	+	+
	M	9				+	+	+	+	+	+	—	—
Berliner [6b]	M	5	?	?	?	?	?	+	+	?	+	?	+
	F	1	?	?	?	?	?	+	+	?	+	?	+
	M	6	?	?	?	?	?	+	+	+	+	?	+
Nissler, K.: Monatschr. f. Kinderh. **80**: 271, 1939	?	7	?	?	?	?	?	+	+	+	+	+	+
Meyer and Okner [1]	F	7	?	1	—	—	+	+	+	+	+	+	+
Hőra, J.: Virchows Arch. f. path. Anat. **305**: 298, 1939	M	0	?	?	?	?	—	+	+	?	+	?	+
Henderson, J. L.: Arch. Dis. Childhood **15**: 201, 1940	M	2	5	3	—	+	+	+	+	+	+	?	+
	M	3				+	+	+	+	+	+	+	+
	F	2				+	+	+	+	+	+	+	—
	M	3	3	2	+	+	+	+	+	+	+	+	+
	F	2				+	+	+	+	+	+	+	+
Ellis [3]	F	2	0	1	—	±	+	+	+	+	+	+	+
Gillespie, P. B., and Siegling, J. A.: J. Bone & Joint Surg. **22**: 171, 1940	F	2	3	1	—	+	+	+	+	+	+	?	+
Waardenburg, P. J.: Ophthalmologica **99**: 307, 1940	F	5	0	1	+	+	+	+	+	+	+	+	+
	M	1	0	1	—	+	+	+	+	?	+	?	+
van Westrienen, A.: Nederl. tijdschr. v. geneesk. **84**: 3459, 1940	M	1	?	?	?	+	—	+	+	+	+	—	—
Stoeckel, K. H.: Monatschr. f. Kinderh. **86**: 348, 1941	M	8	?	?	?	+	+	+	+	+	+	+	+
	F	4	?	?	?	+	+	+	+	+	+	+	+
Hässler [9]	M	3	0	1	?	+	+	+	+	+	+	+	+
	M	10	2	2	?	+	+	+	+	+	+	?	—
	M	3	1	1	?	+	+	+	+	+	+	+	+

TABLE 3.—*Family and Clinical Data in Cases of Gargoylism Reported in the Literature—Continued*

Author	Sex	Age	Sibs		Consanguinity	Mental Defect	Dwarf	Bone Changes				Hepatosplenomegaly	Corneal Clouding
			N	A				Skull	Face	Spine	Limbs		
Veasey, C. A., Jr.: Arch. Ophth. **25**: 557 (April) 1941	M	2	?	?	?	+	+	+	+	+	+	?	+
Ross, and others: Arch. Dis. Childhood **16**: 71, 1941	F	4	?	2	?	+	+	+	+	+	+	+	+
	F	3				+	+	+	+	+	+	+	+
	M	9	?	2	?	+	+	+	+	+	+	+	+
	M	4				+	+	+	+	+	+	+	—
Scharf [21a]	M	28	1	1	+	+	+	+	+	+	+	—	+
Hubeny, M. J., and Deiano, P. J.: Am. J. Roentgenol. **46**: 336, 1941	M	7	?	?	?	—	+	+	+	+	+	?	—
Arnoldson, H., and Nordenson, N. G.: Nord. med. **13**: 603, 1942.	M	14	2	1	—	+	—	+	+	+	+	+	—
Harvey, R. M.: Am. J. Roentgenol. **48**: 732, 1942	M	5	1	1	?	+	+	+	+	+	+	+	+
Cordes, F. C., and Hogan, M. J.: Arch Ophth. **27**: 637 (April) 1942	F	4	1	2	?	+	+	+	+	+	+	+	+
	F	5				+	+	+	+	+	+	+	+
	F	8	?	?	—	+	+	+	+	+	+	+	+
	M	5	1	2	?	+	+	+	+	+	+	+	+
	M	3				+	+	+	+	+	+	+	+
Böcker [21b]	F	3	0	1	+	+	+	+	+	+	+	+	+
Halperin and Curtis [21c]	M	4	2	1	—	+	+	+	+	+	+	+	+
	F	12	3	6	+	+	+	—	+	—	+	—	—
	M	17				+	+	—	+	—	+	—	—
	F	22				+	+	—	+	—	+	—	—
Jervis [24]	M	11				+	+	—	+	—	+	—	—
	F	17				+	+	+	+	—	+	—	—
	M	5				+	+	—	+	?	+	?	?
Breiter, C.: Kinderärztl. Praxis **13**: 60, 1942	F	3	1	1	—	+	+	+	+	+	+	+	+
	M	1	3	1	—	+	+	+	+	+	+	+	+
Lahdensau, S.: Monatschr. f. Kinderh. **92**: 340, 1943	M	8	3	4	?	—	+	+	+	+	+	+	—
	F	6				?	+	+	+	?	+	+	?
	F	19				—	+	+	+	+	+	+	—
	F	16				?	+	+	+	?	+	?	—
Boldt, L.: Ztschr. f. Kinderh. **63**: 679, 1943	M	5	1	1	—	+	—	+	+	+	+	—	+
Nöller [2]	M	43	2	1	—	—	+	+	+	+	+	—	+
Larson, S., and Lichty, J. A.: Am. J. Roentgenol. **50**: 61, 1943	M	3	2	1	?	+	—	+	+	+	+	+	—
	M	1	0	2	?	+	—	+	+	+	+	?	?
	M	1				?	—	+	+	+	+	?	?
Jacottet, M.: Am. pediat. **160**: 11, 1943	F	2	1	1	+	+	—	+	+	+	+	+	+
Rojas Dominguez, J.: Rev. Mex. de pediat. **13**: 261, 1943.	M	7	1	1	—	+	—	+	+	—	+	+	—
Exposito Martinez, L., and de Feria, A.: Bol. Soc. cubana de pediat. **15**: 1113, 1943	M	10	0	2	—	—	+	+	+	+	+	—	+
	F	8				?	—	+	+	+	+	—	+

Author	Sex	Age	Sibs N	Sibs A	Consanguinity	Mental Defect	Dwarf	Bone Changes: Skull	Bone Changes: Face	Bone Changes: Spine	Bone Changes: Limbs	Hepato-splenomegaly	Corneal Clouding
Rojas Domínguez, J.: Rev. Mex. de pediat. **13**: 861, 1943.	M	7	1	1	—	+	—	+	+	—	+	+	—
Exposito Martinez, L., and de Feria, A.: Bol. Soc. cubana de pediat. **18**: 1113, 1943	M	10	0	2	—	—	+	+	+	+	+	—	+
	F	8				?	—	+	+	+	+	—	+
Lurie, L. A., and Levy, S.: Am. J. M. Sc. **207**: 184, 1944	M	7	1	2	—	+	—	+	+	+	+	+	—
	M	6				+	+	+	+	+	+	+	—
Wolff [214]	M	7	5	1	—	+	+	+	+	+	+	+	+
Sear, H. R., and Maddox, J. K.: M. J. Australia **32**: 488, 1945	F	2	1	1	+	+	+	+	+	+	+	+	+
Sawyer, G. M.: J. Iowa M. Soc. **35**: 359, 1945	M	19	?	?	?	+	+	+	+	+	+	+	+
Brouwer-Frommann, H. M.: Nederl. tijdschr. v. geneesk. **90**: 705, 1946	F	2	1	1	?	+	—	+	+	+	+	+	+
Naja, A.: Acta pædiat. **33**: 267, 1946	M	4	0	1	—	+	—	+	+	+	+	?	—
	M	9	0	2	—	+	+	+	+	+	+	+	?
	M	?				+	+	+	+	+	+	+	?
	M	2	0	1	—	+	—	+	+	+	+	+	—
	F	4	0	1	—	+	—	+	+	+	+	+	+
Debré, R., and others: Semaine d. hôp. Paris **22**: 309, 1946	F	10	?	?	?	+	—	—	+	+	+	+	—
	M	7	0	2	?	+	+	+	+	—	+	+	—
	F	4	1	1	—	+	+	+	+	+	+	+	+
Strauss and others [7]	M	18	3	1	—	—	—	+	+	—	+	+	—
Lundström, R.: Nord. med. **33**: 41, 1947	F	6	2	1	—	+	+	+	+	+	+	+	—
	M	12	2	2	—	+	+	+	+	+	+	+	—
	M	6				+	+	+	+	+	+	+	—
Lahey, M. E., and others: J. Pediat. **31**: 220, 1947	F	3	?	?	—	+	+	+	+	+	+	+	+
Strauss [6c]	F	3	1	1	+	+	+	+	+	+	+	+	+
Lindsay and others [23]	M	2	0	1	?	+	+	+	+	+	+	—	+
	M	1	?	?	?	+	+	+	+	+	+	+	—
	M	7	?	?	?	+	+	+	+	+	+	+	+
	F	3	2	1	—	—?	+	+	+	?	+	+	?
	M	4	?	2	+	+	+	—	—	?	+	+	+
	M	1	0	1	—	+	+	+	+	+	+	+	+
Wiedemann, H. R.: Helvet. pædiat. acta. **4**: 77, 1949	F	11	2	1	—	+	+	+	+	+	+	—	+
Present cases	F	10	0	1	—	+	+	+	+	+	+	+	+
	F	5	0	2	—	+	+	+	+	+	+	+	+
	M	7				+	+	+	+	+	+	+	+
	F	6	0	2	—	+	+	+	+	—	+	+	—
	F	6				+	+	+	+	—	?	+	—
	M	6	2	1	—	+	+	+	+	+	+	—	—
	M	5	4	1	—	+	+	+	+	+	—	+	—
	M	5	1	1	—	+	+	+	+	+	—	+	—
	M	10	1	1	—	+	—	+	+	+	—	—	—
	F	3	1	1	—	+	+	+	+	—	+	+	—

The family data concern the number of normal sibs (N) and the sibs affected with gargoylism (A) in the fraternity, and the presence (+) or absence (—) of consanguinity among parents of patients. In no case were the parents affected with gargoylism.

The main clinical features are grouped under four headings, as described in the first section of this paper, but no attempt at a quantification of the symptoms has been made.

In some earlier reports in the literature, the description is so incomplete that doubt may arise as to the diagnosis. In a few other instances it is possible that the same case was reported twice by different authors. These discrepancies, however, are not likely to affect significantly the conclusions of the clinical and genetic discussions, which are based chiefly on the data collected in this appendix.

PERCEPTION OF GONADAL PAIN IN PARAPLEGIC PATIENTS

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FEW REFERENCES deal with the segmental level at which afferent pain-conducting pathways from the testis and epididymis reach the spinal cord. The upper level of this inflow still seems to be a matter of controversy (Mitchell,[1] Pitkin [2]), and it appeared justified, therefore, to study this problem in 53 cases with various levels of traumatic lesions of the spinal cord.

DISTRIBUTION

The injury in 21 cases (40 per cent) was caused by shell fragments or bullets and in 32 cases (60 per cent) by closed injuries (fractures) of the spine. In 9 cases the lesions were cervical, in 38 thoracic and in 6 lumbar. In 14 (25 per cent) the lesions were considered clinically incomplete, and in 39 (75 per cent), as clinically complete. The age distribution was 23 to 58 years. The time interval between injury and examination varied from three months to 6 years. Mild to severe increased reflex activity was observed in 31 cases.

METHOD OF EXAMINATION

Sensation for light touch and pinprick was tested in each case, but only the level for pinprick was used for correlation with the gonadal sensation. The latter modality was tested by squeezing the structures individually (testis, epididymis and vas deferens) between the forefinger and the thumb. The greatest sensitivity was found in the rete testis. Sensation of the covering skin was tested by pinprick or pinching. During these tests the abdominal musculature was observed for reflex contraction.

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Sponsored by the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the author are the result of his own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

1. Mitchell, G. A. G.: The Innervation of the Kidney, Ureter, Testicle and Epididymis, J. Anat. **70**:10-32, 1935; Innervation of the Ovary, Uterine Tube, Testis and Epididymis, ibid. **72**:508, 1937.

2. Southworth, J. L., and Hingson, R. A.: Conduction Anesthesia: Clinical Studies of George P. Pitkin, Philadelphia, J. B. Lippincott Company, 1946.

The sweating response was tested in 37 cases by means of dry heat and direct inspection of perspiration. The results were charted on Keegan's [3] dermatome map. The sweating chamber of Guttmann was used with minor modifications.

Seven of the patients with strong reflex contraction of the abdominal muscles from testicular stimulation were observed fluoroscopically in order to study activity of the diaphragm after stimulation of the testis, epididymis or vas deferens on each side.

RESULTS

The tenth thoracic dermatome appeared to be the critical level for pain of testicular origin. Gonadal pain was absent if the dermatome level for pinprick was higher than the tenth thoracic. All patients with levels for pinprick sensation at the tenth thoracic dermatome or below, with 4 exceptions (fourth thoracic dermatome incomplete lesion; ninth, tenth and twelfth thoracic dermatomes, complete lesions) perceived gonadal pain. In 1 case in which there was analgesia below the ninth thoracic dermatome on the left and between the tenth and the eleventh thoracic dermatome on the right, the left testis was sensitive, whereas the right testis was analgesic. Pain was not equally produced over the testis, epididymis and vas deferens; the testis was most sensitive and the vas least so. Less pressure was needed to produce pain from the testis and epididymis as the level for pinprick descended below the tenth thoracic. The vas, however, was found to be sensitive in only 11 cases. In 2 of these cases the level for pinprick was the tenth thoracic; in the rest it was at lower dermatomes. The results in these 7 cases were equivocal, owing to the possible stimulation of somatic nerves (external spermatic and anterior scrotal) below the level of the twelfth thoracic dermatome.

Whereas the relation of gonadal pain to the level of pinprick was obvious, the relation of gonadal pain to sweating was not so clearly defined. Only when the extent of sweating, rather than the intensity, was considered was it found that a relation between gonadal pain and sweating could be established. Sweating was graded as normal or decreased in intensity or as absent. Sweating tests were carried out in 37 cases; in 19 cases with gonadal sensation intact the level for pinprick was at the tenth thoracic dermatome or lower. In all but 1 of these cases the sweating level (of at least decreased intensity) was at or below the first lumbar dermatome. In 2 cases there were a level for pinprick at the ninth and tenth and the tenth thoracic dermatomes, respectively, and completely normal sweating without gonadal sensation. In the remaining 16 cases without gonadal sensation and with a level for pinprick above the tenth thoracic dermatome (with 2 exemptions), tests revealed sweating above the first lumbar dermatome.

3. Keegan, J. J.: Dermatome Hypalgesia with Posterolateral Herniation of Lower Cervical Intervertebral Disc, J. Neurosurg. 4:115-139, 1947.

An abdominal contraction of jackknife type when the gonads were squeezed was observed in all but 8 of the 53 cases. This contraction was almost always bilateral when either gonad was compressed, but on rare occasions it was confined to the ipsilateral musculature. In the 8 cases without abdominal contraction on stimulation of the gonads the levels for pinprick were between the seventh cervical and the eleventh thoracic dermatome. In all but 2 cases there was flaccid paralysis. In these 2 cases the deep abdominal reflexes were decreased, and in 1 of them sensation was preserved on stimulation of the left gonad only. In another case in this group there was unilateral (left) gonadal sensation, but in this case there was flaccid musculature also. The degree of general hyperreflexia appeared responsible for the intensity of this "jackknife" response, rather than pain perception from the gonads. In 7 cases fluoroscopic examination was made while the "jackknife" reflex was being tested. In all 7 cases respiratory movement of the diaphragm was normal. In 3 cases examination revealed passive elevation of the central portion of the diaphragm during the contraction of the abdominal musculature, while in 4 it showed no abnormal diaphragmatic activity.

COMMENT

The gonads and their tunicae are supplied by both autonomic and somatic nerves.[3a] The autonomic component involves the internal spermatic nerve. The somatic elements are composed of (*a*) the external spermatic nerve, a branch of the genitofemoral nerve (first and second lumbar nerves); (*b*) the anterior scrotal nerve, originating from the ilioinguinal (first lumbar nerve), and (*c*) the posterior scrotal nerve, which branches off from the pudendal nerve (second, third and fourth sacral nerves).

Mitchell [1] described the autonomic nerve supply and distinguished superior, middle and inferior spermatic nerves. The superior spermatic nerve originates in the renal plexus and intermesenteric nerves and supplies only the testis. The middle and inferior spermatic nerves derive from the hypogastric plexus, the hypogastric nerves and the pelvic (inferior hypogastric) plexus and innervate the epididymis and the vas deferens.

There is still controversy regarding the segmental level at which pain-conducting fibers from the gonads reach the cord. Older authors (Lennander and MacKenzie, cited by Lewis[4]) denied the presence of

3a. Kuntz, A.: The Autonomic Nervous System, ed. 3, Philadelphia, Lea & Febiger, 1945. Möller, J., and Müller, P.: Grundriss der Anatomie des Menschen für Studium und Praxis, Berlin, W. de Gruyter & Co., 1933. Toldt, C.: Anatomischer Atlas, für Studierende und Aerzte, edited by D. F. Hochstetter, ed. 12, Berlin, Urban & Schwarzenberg, 1923.

4. Lewis, T.: Pain, New York, The Macmillan Company, 1942.

pain fibers in the testis or epididymis and suggested that the tunica vaginalis contained receptors of pain. It is now recognized (Brown,[5] Mitchell,[1] Pitkin [2]) that pain can originate in the gonads proper. Pain fibers were said to reach the cord at the ninth thoracic dermatome and higher (Mitchell), a statement apparently based on one observation of Learmonth's and another of Mitchell's on patients during spinal anesthesia. It was also proposed that a possible, though not proved, pathway may exist via the phrenic ganglion, phrenic nerves and intrathoracic autonomic chain. Our experience, rather, supports Pitkin's observation with use of segmental anesthesia which indicated that the tenth thoracic dermatome was the upper level for the elimination of pain from the gonads.

Our findings also confirm Brown's observation that referred pain from the testis is felt by the patient in the region of the deep inguinal ring and anterosuperior aspect of the iliac crest, and not in the tenth thoracic dermatome. Both these facts, the upper level of pain perception coinciding with the tenth thoracic dermatome and the site of referred pain, are consistent with the embryonic development of segmental innervation in this region. Pitkin demonstrated that sensation of pain from the testis can be blocked by anesthesia of the tenth and eleventh thoracic segments, while the eleventh and twelfth thoracic and the first lumbar segments must be interrupted if pain is to be eliminated in the epididymis. Although an analgesiometer was not used to measure the pressure necessary to produce pain, it was noted that sensibility to squeezing increased as the paraplegic level descended from the tenth thoracic to the first lumbar dermatome, indicating a multiple segmental supply. Obviously, additional pain from the tunica vaginalis is perceived in lesions with a segmental level below the twelfth thoracic dermatome.

Previous experience suggested strongly a correlation between the level of injury to the spinal cord as manifested by alteration in sweating and histologic evidence of testicular atrophy in paraplegic patients (Bors, Engle, Rosenquist and Holliger [6]). With expansion of this observation in the present study, gonadal pain was found to be correlated with the level of sweating. Obviously, the functions involved were quite different in that sweating was mediated by efferent and pain sensitivity by afferent fibers. Indeed, this difference seemed to be substantiated when it was noted that the level of normal sweating showed no correlation with pain perception. However, if areas of decrease in, as well as absence of, sweating were included in the evaluation, a relation between efferent cholinergic and afferent pain

5. Brown, F. R.: Testicular Pain: Its Significance and Localization, Lancet **1**:994-999, 1949.

6. Bors, E.; Engle, E. T.; Rosenquist, R. C., and Holliger, V. H.: Unpublished data.

fibers became apparent. All but 1 of 19 patients with sensitive gonads and a level for pain perception at the tenth thoracic dermatome or lower revealed traces of sweating to the first lumbar dermatome, or even lower. The first lumbar dermatome, therefore, was the uppermost level of sweating at which sensitivity of the gonads appeared. We do not imply that these two functions are mediated by the same pathways; yet it is an interesting coincidence that the first lumbar dermatome was reported by Pitkin as the lowermost pain level for the epididymis.

A "jackknife" reflex can be observed when gonadal sensation is present and appears as a complex movement in response to a "sham attack" on the gonads of normal persons. In patients with spinal cord injuries this reflex is chiefly confined to the reflex activity of the musculature below the level of the lesion and is therefore subject to exaggeration or decrease, depending on the condition of the cord. In rare cases does this reflex occur in its simplest form, namely, unilaterally from stimulation of the ipsilateral testis; usually the response is bilateral from stimulation of either gonad. Its presence depends only on a functioning reflex arc, and not on the presence of gonadal sensation. The response could not be proved to involve actively any part of the diaphragm on fluoroscopic observation, not even the lateral pillars, which, according to Favill,[7] derive their motor and sensory innervation from the seventh to the twelfth thoracic segments, even though a contraction of the abdominal muscles, supplied by these segments, was clearly visible. However, it is just this abdominal contraction which makes fluoroscopic determination difficult. The upward movement of the central portion of the diaphragm observed in 3 cases can be explained best as a passive mechanical bulging because the abdominal cavity is compressed by the contracting abdominal muscles. This "jackknife" reflex could be produced only once from stimulation of the vas deferens. This observation must be regarded with reserve, however, because it is difficult to squeeze the vas deferens without exerting a pull on the spermatic cord and gonads, which in itself suffices to elicit the reflex.

SUMMARY

Stimulus sufficient to produce pain in the gonads was given in 53 cases of paralysis due to injury to the spinal cord. Sweating tests were combined with studies of pain perception in 37 of these cases. The following observations were made:

7. Favili, J.: Outline of the Spinal Nerves, Springfield, Ill., Charles C Thomas, Publisher, 1946.

1. The tenth thoracic dermatome for sensation of pinprick was consistent as the upper level at which gonadal pain could be perceived.

2. The intensity of gonadal pain appeared to increase as the level for pinprick descended below the tenth thoracic to the upper lumbar segments.

3. Gonadal pain was present in 19 cases when some sweating could be demonstrated at the first lumbar dermatome, but not above.

4. An abdominal "jackknife" reflex was present on gonadal stimulation as long as the reflex arc functioned. It was present also in the absence of gonadal sensation, and its intensity depended on the degree of the general state of reflex activity.

The results are discussed in the light of the literature.

Dr. John D. French gave valuable assistance in preparing this paper, and Dr. Roy H. Nyquist performed the sweating tests.

SECTION OF CORPUS CALLOSUM IN EXPERIMENTAL EPILEPSY IN THE MONKEY

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THE EFFECT of section of the corpus callosum on human epilepsy remains a controversial issue. Van Wagenen and Herren [1] found that in patients with generalized convulsions section of commissural pathways contained in the corpus callosum limited the spread in a unilateral convulsion with no loss of consciousness. Erickson,[2] using electrical stimuli, showed that in the monkey section of the corpus callosum played a definite role in the spread of a discharge from one hemisphere to the other. Curtis [3] concluded that the typical response to the application of a convulsant drug in monkeys and cats was mediated by the corpus callosum and abolished by its section. Obrador Alcalde,[4] studying convulsive attacks produced by electrical stimulation of the cortex in cats, reported that section of the corpus callosum did not change the fundamental character of the convulsions and concluded that the

Read by title at the Seventy-Fifth Annual Meeting of the American Neurological Association, Atlantic City, N. J., June 13-15, 1948.

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1. Van Wagenen, W. P., and Herren, R. Y.: Surgical Division of Commissural Pathways in the Corpus Callosum: Relation to Spread of an Epileptic Attack, Arch. Neurol. & Psychiat. **44**:740 (Oct.) 1940.

2. Erickson, T. C.: Spread of the Epileptic Discharge: An Experimental Study of the After-Discharge Induced by Electrical Stimulation of the Cerebral Cortex, Arch. Neurol. & Psychiat. **43**:429 (March) 1940.

3. Curtis, H. J.: Intercortical Connections of the Corpus Callosum as Indicated by Evoked Potentials, J. Neurophysiol. **3**:407 (Sept.) 1940.

4. Obrador Alcalde, S.: Corpus Callosum and Epileptic Fits, Bol. Laborat. estud. méd. méx. **1**:29 (March) 1942.

corpus callosum was not an association system essential to the transmission of epileptic attacks. In an investigation of the conduction of cortical impulses and a review of the literature, Hoefer and Pool [5] found that section of the corpus callosum in cats and monkeys caused a rise in the convulsive threshold and appeared to shorten the duration of seizures produced by means of electrical stimulation. They observed that during generalized seizures in such instances cortical discharges were equal on the two sides.

In our previous work,[6] we demonstrated that the application of aluminum oxide (alumina) cream [7] to one motor cortex of the monkey induced recurrent epileptiform seizures. The onset, after a latent interval of three to twelve weeks, was characterized by contralateral jacksonian seizures. These attacks increased in severity and usually became bilateral. Electroencephalograms indicated the development of a focus of abnormality in the region of application of the inciting agent, with subsequent spread to other areas of the brain, particularly to the contralateral homologous region.[7a] Abnormal tracings were characterized by frequent bursts of high voltage slow activity and a varying incidence of spike potentials. At times spike-wave complexes appeared. The slow waves often exhibited distortions in contour, and many sharp formations and irregular features were noted. The abnormal activity, and particularly the spike potentials, were most prominent in the region of the inciting agent. The recent report of Pope and his collaborators [8] is of particular interest in this connection, since they also recorded similar spikes and sharp waves from focal epileptogenic lesions produced by aluminum oxide cream in monkeys, as well as a secondary activation of the contralateral homologous cortical area.

Because of the clinical progression in our monkeys from unilateral to bilateral attacks with a corresponding spread of electroencephalo-

5. Hoefer, P. E. A., and Pool, J. L.: Conduction of Cortical Impulses and Motor Management of Convulsive Seizures, Arch. Neurol. & Psychiat. **50**:381 (Oct.) 1943.

6. (*a*) Kopeloff, L. M.; Barrera, S. E., and Kopeloff, N.: Recurrent Convulsive Seizures in Animals Produced by Immunologic and Chemical Means, Am. J. Psychiat. **98**:881 (May) 1942. (*b*) Kopeloff, N.; Kopeloff, L. M., and Pacella, B. L.: The Experimental Production of Epilepsy in Animals, in Hoch, P. H., and Knight, R. P.: Epilepsy: The Psychiatric Aspects of Convulsive Disorders, New York, Grune & Stratton, Inc., 1947, p. 163.

7. The preparation used was a mixture of hydrous aluminum oxides.

7a. Pacella, B. L.; Kopeloff, N.; Barrera, S. E., and Kopeloff, L. M.: Experimental Production of Focal Epilepsy, Arch. Neurol. & Psychiat. **52**:189 (Sept.) 1944.

8. Pope, A.; Morris, A. A.; Jasper, H.; Elliott, K. A. C., and Penfield, W.: Histochemical and Action Potential Studies on Epileptogenic Areas of Cerebral Cortex in Man and the Monkey, A. Research Nerv. & Ment. Dis., Proc. **26**:218, 1946.

graphic abnormality, the present study was undertaken to determine the effect of section of the corpus callosum (*a*) in monkeys in which bilateral seizures had been established and (*b*) in monkeys in which section had been made prior to the application of aluminum oxide cream.

PRESENT INVESTIGATION

The corpus callosum was sectioned in 7 animals. Sections were performed in 4 monkeys after bilateral seizures had developed after unilateral application of aluminum oxide cream. In 3 monkeys the corpus callosum was sectioned approximately three months prior to the application of aluminum oxide cream to one motor cortex. Electroencephalograms were taken by the method previously reported.[7] At the termination of the experiment the animals were killed and the

TABLE 1.—*Effect of Section of Corpus Callosum in Epileptic Monkeys*

Monkey No.	Cortical Area of Aluminum Oxide	Onset of Seizures, Months	Duration of Seizures, Months: Contralateral	Duration of Seizures, Months: Bilateral	Maximal Electroencephalographic Abnormality: Left	Maximal Electroencephalographic Abnormality: Right	Result of Section of Corpus Callosum	Extent of Section	Position of Disk
450	Left motor	3	9	5	++±	++	Status epilepticus (right side) 4 days later; monkey died on 6th day	Complete except for posterior 3 mm.	Fig. 1 *A*
502	Left motor	2	8	2½	+++	++	Status epilepticus (right side) 1 day later, lasting to 8th day; monkey died on 13th day	Unavailable	
485	Left motor	1½	5	¼	+++	+	First section: right-sided seizures	Incomplete posteriorly	
			6*	..	++++	++	Second section, 2 years later: no further seizures	Complete	Fig. 1 *B*
			0	..	++++	+			
437A†	Right motor	2	15	13½	++++	++++	Brief left-sided attack 4 days later; on 5th to 7th day, status epilepticus (left side); monkey died on 8th day	Complete except for anterior 2-3 mm. of callosum	Fig. 1 *C*

* Fifteen months after first section, two abortive seizures (clonic movements of the right arm).
† Cortical ablations were performed in infancy (three years before application of aluminum oxide cream): Incomplete ablation of area 6 and partial removal of the anterior part of the caudate nucleus were performed bilaterally.

brains studied anatomically. Individual maps are included to illustrate the position of the aluminum oxide cream disk.[9]

Section of Corpus Callosum in Epileptic Monkeys.—In 4 monkeys in which recurrent bilateral seizures had been established for various periods, section of the corpus callosum was performed. A summary of the pertinent data is presented in table 1.

All subsequent seizures in the monkeys so treated were restricted to the side opposite the original application of the inciting agent. In 3 of the 4 animals these unilateral attacks increased in frequency and severity, culminating in unilateral status epilepticus and death within

9. von Bonin, G., and Bailey, P.: The Neocortex of Macaca Mulatta, Illinois Monographs in the Medical Sciences, Urbana, Ill., University of Illinois Press, 1948, vol. 4, no. 4.

thirteen days after section of the corpus callosum (electroencephalograms not obtained). In the fourth monkey (485), after an asymptomatic interval of four and one-half months, seizures were subsequently elicited for a period of six months but were confined to the contralateral side. In the same animal, because of the persistence of electroencephalographic abnormality in the opposite hemisphere, surgical exploration of the section of the corpus callosum was made at a second operation, when a small portion of the posterior part of the splenium was found to be intact. Since this may have accounted for the spread of the electroencephalographic abnormality observed after the first section of the corpus callosum, it was severed and the animal observed for seventeen months. Clinically, no seizures could be elicited. Nevertheless, there

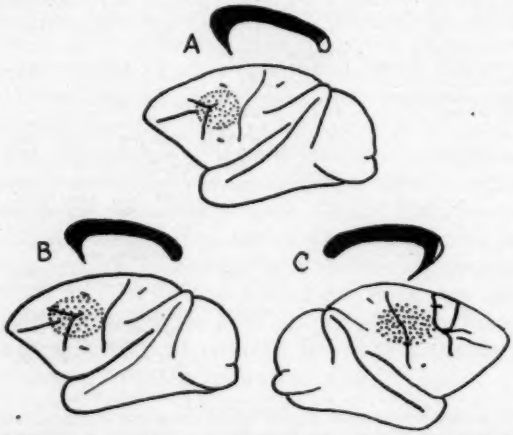

Fig. 1.—The position of the aluminum oxide cream disk is indicated by the dotted area over the precentral motor region. The shaded portion of the corpus callosum indicates the extent of section which was performed after seizures had been established. In *C* the ablated frontal area of one side is outlined.

was only slight diminution in the degree of spread of the abnormal discharges to the opposite side, whereas pronounced electroencephalographic abnormality persisted over the original focal area for the duration of the experiment.

In monkey 450 postmortem examination disclosed that section of the corpus callosum was complete except for the posterior 3 mm. of the splenium. The brain of monkey 502 was unavailable for examination. In monkey 485 section was complete in the midsagittal plane. In monkey 437 A section of the corpus callosum was complete except for the anterior 2 or 3 mm. The position of the disk in the motor region is indicated in figure 1.

Section of Corpus Callosum Prior to the Production of Epilepsy.—In 3 animals in which section of the corpus callosum was performed, electroencephalograms revealed no significant changes for a preliminary observation period of one to four months. Aluminum oxide cream was then applied to one motor cortex. It may be seen in table 2 that the subsequent development of seizures was restricted to the contralateral side for the duration of the experiment. In monkeys 492 and 500 the attacks were severer and much more easily elicited than those observed in a large series of animals similarly treated but without section of the corpus callosum. Marked electroencephalographic abnormalities, consisting chiefly of high voltage slow activity and spike

TABLE 2.—*Effect of Section of the Corpus Callosum in the Monkey Prior to Production of Epilepsy*

Monkey No.	Extent of Section of Corpus Callosum	Time (After Section) of Application of Aluminum Oxide Cream to Right Motor Cortex, Mo.	Seizures			Maximal Electroencephalographic Abnormality		Position of Disk
			Onset, Mo.	Type	Duration, Mo.	Left	Right	
492	Nearly complete; posterior 3 mm. of splenium intact	1	3	Left side	18	±	+++±	Fig. 4 *A*
500	Nearly complete; posterior 3 mm. of splenium intact	2	1½	Left side	12	+	+++	Fig. 4 *B*
503	First section Second section* anterior 8 mm. of corpus callosum intact	4	2	Left side None	5	++ ++	+++ +++	Fig. 4 *C*

* Resection of the corpus callosum was performed one year after original section, with no further seizures or significant changes in the electroencephalographic pattern. Extensive scarring of the medial portion of the convexity and the adjacent mesial surface of the left cerebral hemisphere was observed at autopsy.

potentials, were noted over the site of application of the aluminum oxide cream, while some abnormality was found in the opposite hemisphere, especially posteriorly. The development of electroencephalographic abnormality is indicated in figures 2 and 3.

Examination of the brains of these animals indicated that section of the corpus callosum was complete except for 3 to 4 mm. of the posterior part of the splenium. The position of the aluminum oxide cream disk is shown in figure 4.

In the third monkey (503) section of the corpus callosum again restricted seizures to the contralateral side. However, contrary to the results in the 2 monkeys just described, the attacks were less frequent and less severe. Since the electroencephalograms showed considerable spread of abnormality, there was some question concerning the complete-

ness of section. Consequently, a further attempt was made to sever any remaining fibers in the corpus callosum. Except for a few clonic movements in the contralateral limbs three and one-half months later, this monkey failed to exhibit further seizures for the subsequent period of observation (fifteen months). After resection, mild spread of focal

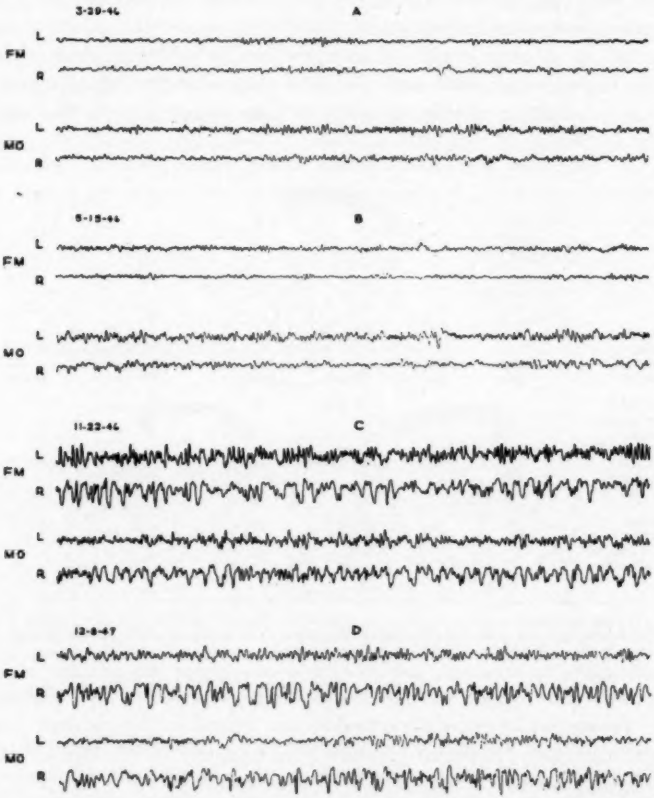

Fig. 2 (monkey 492).—*A*, control tracing, a normal record with considerable alpha rhythm. *B*, five weeks after section of the corpus callosum; the record is similar to *A*. *C*, six months after application of aluminum oxide cream to the right precentral motor cortex; the record shows considerable slow and fast activity with spikes on the right and minimal spread of slow potentials to the left. *D*, nineteen months after application of aluminum oxide cream; the record shows marked slowing of activity and spikes persisting on the right, with only occasional minimal spread to the left.

electroencephalographic discharges was still present and most pronounced in the posterior regions, but there was evidence of a gradual

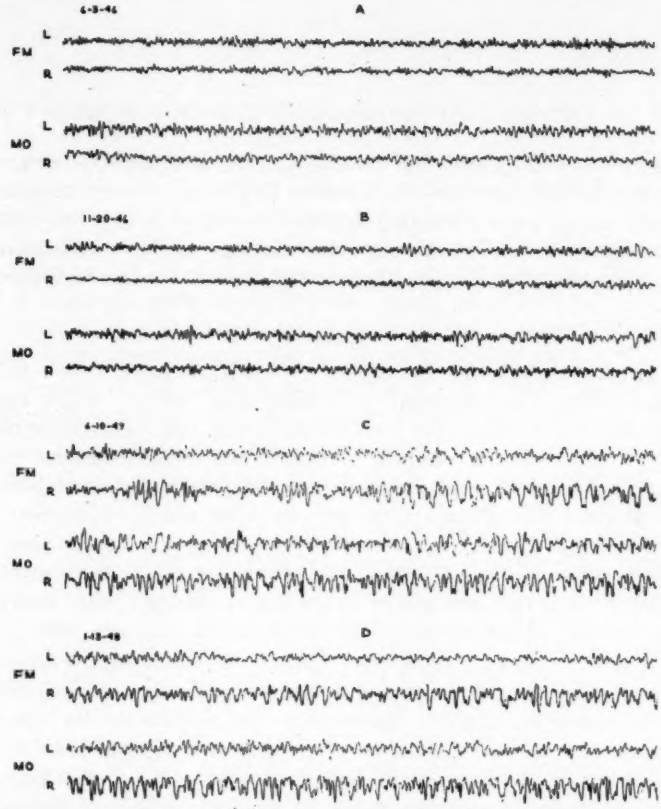

Fig. 3 (monkey 500).—*A*, control tracing, a normal record exhibiting considerable alpha rhythm posteriorly. *B*, five weeks after section of the corpus callosum; the record shows occasional moderate slow potentials, but is otherwise similar to *A*. *C*, six months after application of aluminum oxide cream to the right precentral motor cortex; the record shows considerable high voltage slow and fast activity with spikes on the right and moderate spread to the left. *D*, thirteen months after application of aluminum oxide cream; the record shows activity on the right, similar to that in *C*, but substantial diminution of spread to the left, chiefly in the posterior region.

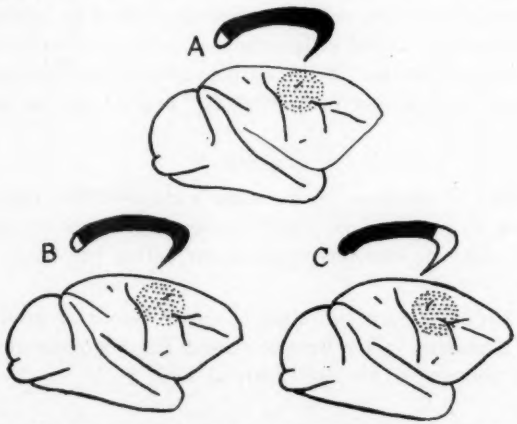

Fig. 4.—In this group section of the corpus callosum preceded the application of aluminum oxide cream (designated by the dotted area). As in figure 1, the shaded portion of the corpus callosum indicates the extent of the section.

diminution. At postmortem examination the most anterior 8 mm. of the corpus callosum was found intact, and extensive cortical scarring of the mesial surface and the adjacent convexity of the left cerebral hemisphere was also observed. This scarring may have accounted for the electroencephalographic abnormality observed on the left side.

COMMENT

In the monkey, the application of aluminum oxide cream to one motor cortex has been found to induce focal epilepsy which closely resembles the human type, both clinically and electroencephalographically.[6b] Extensive or complete section of the corpus callosum, either before application of the cream or after the development of bilateral seizures, has been shown in the present study wholly to restrict subsequent attacks to the contralateral side. It would appear that the corpus callosum plays a major role in the spread of the convulsive discharge from one hemisphere to the other, although other pathways may function in the spread of discharges to the opposite side.

It is to be noted that in every instance in which electroencephalograms were taken after section of the corpus callosum a minimal degree of electroencephalographic abnormality was present in the opposite hemisphere. In the monkeys in which section was made prior to the application of aluminum oxide cream, 3 to 4 mm. of the splenium remained intact, accounting perhaps for the predominance of the spread from one side to the other in the posterior region. Of the group in which section was performed after bilateral seizures had been established, 1 monkey (485), which survived eighteen months after complete section, still exhibited some electroencephalographic abnormality over the contralateral hemisphere.

It is significant that after section of the corpus callosum the unilateral seizures observed were more easily elicited by physical stimuli and were of greater severity than those usually encountered in epileptic monkeys without section of the corpus callosum. This may possibly be attributed to severance of "inhibitory" fibers from the contralateral hemisphere.

SUMMARY

The effect of extensive or complete section of the corpus callosum was studied in monkeys in which the application of aluminum oxide (alumina) cream to one precentral motor cortex preceded or followed section.

1. Section of the corpus callosum either before or after the application of aluminum oxide cream caused the complete restriction of subsequent seizures to the contralateral side.

2. The resulting unilateral attacks were considerably severer and more easily elicited than those observed in a large control series of "epileptic" monkeys with intact corpus callosum.

3. Section of the corpus callosum after bilateral seizures had been established caused status epilepticus on the side opposite the focus in 3 of 4 monkeys, while section of the corpus callosum prior to the application of aluminum oxide cream to one cortex resulted in easily elicited contralateral seizures but not in status epilepticus.

4. Section of the corpus callosum did not completely inhibit the spread of abnormal electrical impulses to the side opposite the focus.

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Miss Mary Szczerba gave technical assistance.

ELECTROMYOGRAPHIC PATTERNS IN REINNERVATED MUSCLE

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EXTENSIVE reports are available concerning the action potentials occurring in normal and denervated muscles.[1] A few investigators have reported the electromyographic changes during the process of reinnervation following section and suture of peripheral nerves. However, these reports have been confined to a relatively short period following the suture. Weddell, Feinstein and Pattle [2] described the changes during this period: (*a*) Fibrillation action potentials decrease in number; (*b*) motor unit action potentials, small in amplitude and highly polyphasic, are the earliest to make their appearance, first close to the motor point and then spreading rapidly throughout the muscle; (*c*) with what the authors term "functional recovery," a few polyphasic units and fibrillation potentials are still present, and the range of amplitude and duration of motor unit responses are greater than in normal muscle. In the cases which they reported in detail, nerve sections were not all complete; the patients were followed for periods too short to assure complete recovery, and, though the authors reported functional recovery,

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Read in part at a meeting of the Eastern Association of Electroencephalography, Dec. 4, 1949, in New York.

This work was done under a contract between the Veterans Administration and Columbia University, on recommendation of the National Research Council.

From the Department of Neurology, Columbia University College of Physicians and Surgeons, and the Neurological Institute of New York and Presbyterian Hospital.

1. Adrian, E. D., and Bronk, D. W.: The Discharges of Impulses in Motor Nerve Fibers: II. The Frequency of Discharge in Reflex and Voluntary Contractions, J. Physiol. **67**:119-151, 1929. Denny-Brown, D. E., and Pennybacker, J.: Fibrillation and Fasciculation in Voluntary Muscles, Brain **61**:311-334, 1939.

2. Weddell, G.; Feinstein, B., and Pattle, R. E.: The Electrical Activity of Voluntary Muscle in Man Under Normal and Pathological Conditions, Brain **67**:178-257, 1944.

the precise meaning of this term was not specified. Jasper [3] reported essentially similar findings and described the complex polyphasic units as being below 500 microvolts in amplitude and lasting 15 to 20 milliseconds, but becoming shorter and larger as reinnervation progressed. However, he did not specify the duration of the period of reinnervation or the extent of motor recovery.

Though these authors agree as to the early signs of reinnervation, they offer no conclusion as to the ultimate electromyographic picture when reinnervation is complete. Working along the same lines, Golseth and Fizzell [4] studied the electromyographic changes in the tibialis anterior muscle in the cat from the time of denervation to what they termed complete functional recovery following section and suture of the sciatic nerve This period of observation was for ninety days after suture. They concluded that complete functional recovery, which is defined as absence of weakness, precedes complete electromyographic recovery. However, it should be pointed out that the work of Berry, Grundfest and Hinsey [5] demonstrated that at 90 days the velocities of conduction in nerve fibers have recovered only to about one-third their normal value. Hence, very slow conduction is to be expected, and with it abnormal electromyographic patterns. Furthermore, in their experiments, even after 466 days normal voluntary use of the affected muscles was not observed. Berry and Hinsey,[6] extending this work for 1,363 days, still noted velocities only 80 per cent of normal, an indication that nerve fibers had not recovered their original diameter. Golseth and Fizzell's criterion for incomplete electromyographic recovery was the finding of fibrillation potentials and polyphasic units in some areas of the muscle. The authors did not describe the over-all electromyographic pattern of these muscles or state what they would consider complete electromyographic recovery.

The electromyographic findings noted have been correlated with a number of anatomic and physiologic changes occurring in muscle during reinnervation. Thus, the multiplicity of phase of these units has been explained by the fact that the fibers constituting these units are scattered throughout the muscle, rather than being contiguous and in discrete bundles, as they are in normal muscle. Also, abnormal ramifications

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4. Golseth, J. G., and Fizzell, J. A.: Electromyographic Studies in Cats After Section and Suture of the Sciatic Nerve, Am. J. Physiol. **150**:558-567, 1947.

5. Berry, C. M.; Grundfest, H., and Hinsey, J. C.: The Electrical Activity of Regenerating Nerves in the Cat, J. Neurophysiol. **7**:103-116, 1944.

6. Berry, C. M., and Hinsey, J. C.: The Recovery of Diameter and Impulse Conduction in Regenerating Nerve Fibers, Ann. New York Acad. Sc. **47**:559-574, 1946.

of terminal axons have variable but slow conduction rates, a fact which may contribute to the irregularity of these spikes. The potentials of low amplitude available from these units are explained by the decreased number of fibers in each unit. With the extensive anatomic changes that take place in reinnervation, it would appear that the electromyographic picture of reinnervated muscle should differ markedly from the normal. The investigations cited failed to establish this, perhaps because they had dealt with intervals of time too short to permit one to assume that the process of reinnervation was terminated. Certainly, the reinnervation is a dynamic process extending over a period of years, and good clinical criteria for its completion are lacking. To study this problem, we investigated the action potentials in muscles in groups of patients having in common section and suture of a peripheral nerve in the extremities 3 to 5 years prior to the present observation. The muscles were tested manually for power; chronaxias were measured, and electromyographic patterns were recorded with the muscles at rest and in volitional contraction.

TECHNIC

A differential high gain, condenser-coupled amplifier and a cathode ray oscillograph were used for the electromyographic[7] studies. Action potentials were visualized on the tube face and simultaneously photographed on 35 mm. film with a camera having speeds up to 60 inches (152 cm.) per second. Coaxial needle recording electrodes were used throughout.

The muscle to be studied was identified manually and electrically and a coaxial needle inserted close to the motor point, as well as in random areas proximal and distal to it. To be certain that the recording tip of the needle was in the muscle under investigation, stimuli were applied through the needle electrode and contraction in the muscle was noted. Recordings were then made with the muscle at rest and with varying degrees of voluntary contraction. In order to insure maximum utilization of the muscle, it was used as a prime mover as well as in associated movements. (The significance of this will be referred to later.) Since the object of this study was to identify individual units in any active area, the needle was moved in various directions until maximum amplitude, shortest duration and smooth, essentially diphasic, contour of the muscle action potential could be derived. Not only did this require many samplings of the muscle, but each sampling had to be fully exploited by rotating the needle in a 180 degree arc in all places before a given locus was discarded. Twelve muscles in the extremities, supplied by five nerves, were studied in this way. In almost all cases the corresponding muscle in the normal extremity was investigated and the results were compared.

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7. The amplifier is a two channel, battery-operated unit with a Toennies differential input stage, developed by one of us (H.G.) for use with the DuMont type 279 double beam oscillograph. The maximum gain available represents a sensitivity of about 0.5 mm. per microvolt. The importance of using a highly differential amplifier cannot be stressed enough. Only amplifiers with such characteristics can insure the sharp localization of activity which has been observed in our work, but which seems not to have been noted in other reports.

OBSERVATIONS

In 76 cases investigated by this technic two outstanding patterns were noted. The first was characterized by spontaneous action potentials of 1 millivolt or less occurring at rest and persisting with voluntary effort. Additional motor unit discharges, smaller in amplitude but simple in form, were noted during voluntary effort. The spontaneous discharges continued with cessation of voluntary effort (fig. 1). The potentials brought in with effort lacked the polyphasic features noted in early reinnervation by other observers. This pattern of large spon-

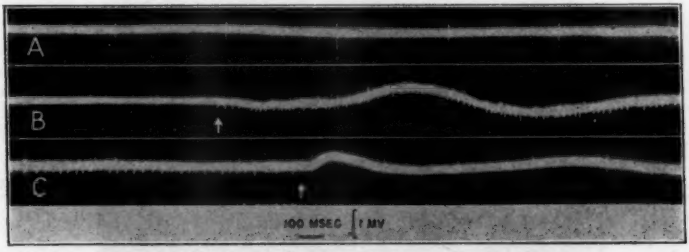

Fig. 1.—Records from the abductor pollicis brevis, at rest and with volitional contraction, four years after suture of the median nerve. *A*, spontaneous action potentials from the muscle at rest; *B*, addition of small action potentials with volitional contraction; *C*, disappearance of small action potentials and continuation of spontaneous potentials with cessation of contraction.

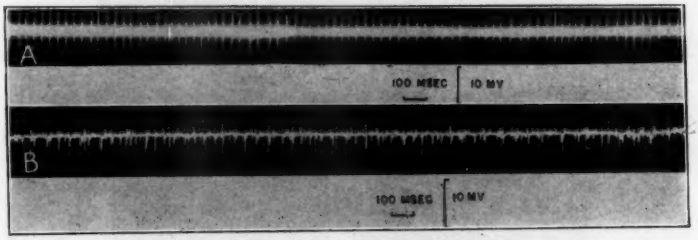

Fig. 2.—*A*, a unitary action potential of 10 millivolts repeated uniformly throughout a voluntary contraction of the abductor digiti quinti. Suture of the ulnar nerve was done three years prior to recording; *B*, occurrence of large spike potential of 10 millivolts, in association with potentials of varying amplitudes. Recording was done during voluntary contraction of the abductor digiti quinti three years after suture of the ulnar nerve.

taneous spikes was not consistent throughout the muscles, as a change in the position of the needle showed areas without spontaneous potentials. However, the pattern was available from a number of areas of the same muscle.

Muscles producing this picture gave only perceptible contraction, too weak when tested manually to perform a movement. Determinations

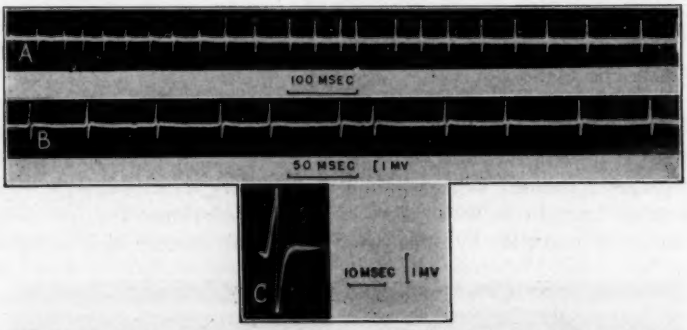

Fig. 3.—*A*, a single action potential of 4 millivolts occurring with voluntary contraction of the tibialis anterior three years after suture of the peroneal nerve. Variation in frequency appeared during contraction. *B*, same potential recorded at twice the camera speed shown in A. *C*, enlargement of spike potential from the record in *B*, showing smooth, nearly diphasic contour and short duration.

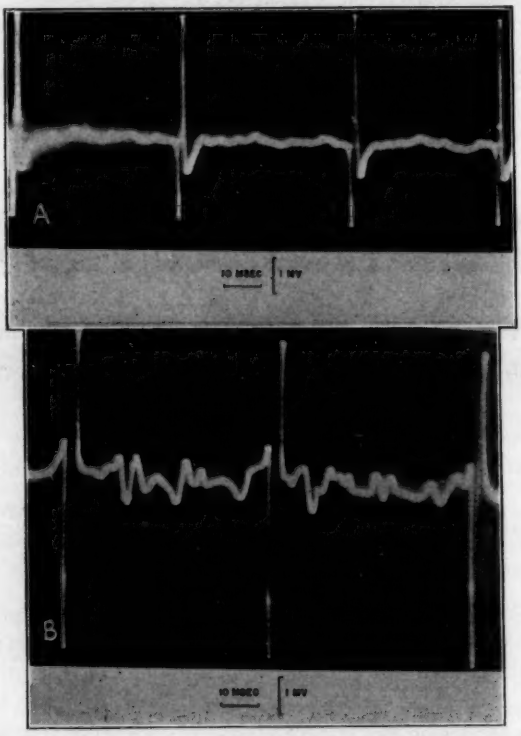

Fig. 4.—Examples of variation in size of action potentials from reinnervated muscle. *A*, action potential of 6 millivolts from the abductor digiti quinti. *B*, action potential of 9 millivolts from the abductor digiti quinti.

of chronaxia in the muscles gave values five to ten times the normal, an indication of partial reinnervation. The basis for this type of pattern is obvious—denervated and reinnervated fibers exist side by side during the process of reinnervation. It is important, however, to note that, even though these observations were made three to five years after suture,

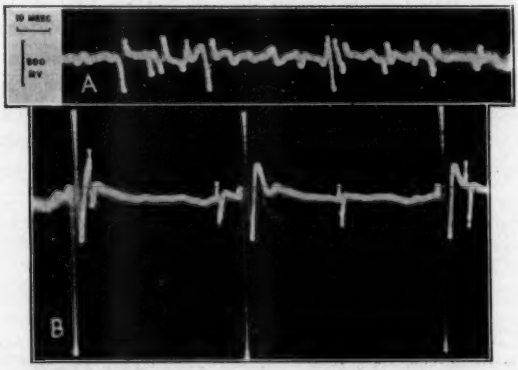

Fig. 5.—Comparative size of action potentials recorded from a normal and from a reinnervated muscle in the same patient. *A*, record from normal abductor digiti quinti during voluntary contraction, showing potentials of 500 microvolts. *B*, record from reinnervated abductor digiti quinti four years after suture of the ulnar nerve. Action potentials during voluntary contraction are five times the normal size.

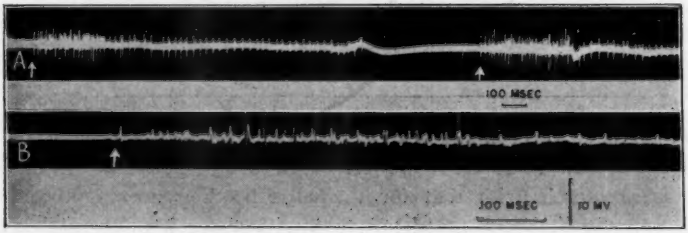

Fig. 6.—Action potentials of 10 millivolts occurring with onset of contraction and fatiguing rapidly. The arrow indicates onset of each contraction. The potentials in *A* were recorded at one-third the camera speed of that in *B*.

muscle fibers that had not regained their nerve supply were still viable and had not been replaced by fibrous tissue.

The second pattern, which comprised the major portion of these tracings, was quite different. This group showed no spontaneous action potentials at rest but a characteristic pattern with volitional contraction. This pattern was distinguished by the occurrence of spikes of very large potential, either alone or in association with many other spikes, of smaller

amplitudes (fig. 2). The large spike potential was a repetitive discharge of uniform amplitude and form that varied in frequency (figs. 2 and 3). Its form was persistently a triphasic spike with two phases predominating to give an essentially diphasic appearance (figs. 3 and 4), but on occasion a slower fourth phase could be noted (fig. 5). Its amplitude was persistently higher than that in normal muscle (fig. 5) but varied in different muscles. Maximum amplitudes plotted in 72 cases showed variations from 2 to 15 millivolts (table). It is also to be noted from this table that the larger amplitudes occurred in the smaller muscles. Comparison of the amplitudes for the abductor pollicis brevis and those for the tibialis anterior muscles, on which an equal number of observations were made, shows that the distribution for the abductor

Distribution of Amplitudes in Twelve Muscles Supplied by Five Peripheral Nerves

	Ulnar			Median			Radial		Peroneal			Tibial	
Amplitude, MV	Abductor Digiti Quinti	First Dorsal Interosseus	Flexor Carpi Ulnaris	Abductor Pollicis Brevis	Flexor Carpi Radialis	Flexor Digitorum Profundus	Extensor Digitorum Communis	Extensor Carpi Radialis	Tibialis Anterior	Peroneus Longus	Extensor Digitorum Longus	Gastrocnemius	Total
1	..	..	..	..	..	..	..	..	..	..	..	..	0
2	1	..	..	..	..	..	1	..	2	..	1	..	5
3	..	1	..	..	..	..	1	..	..	..	..	..	2
4	..	..	..	..	..	..	2	..	2	1	..	..	5
5	3	..	1	..	..	..	..	..	..	..	1	..	5
6	4	..	..	..	..	..	1	1	3	..	..	..	9
7	1	..	..	1	..	1	..	..	1	..	..	1	5
8	1	..	..	3	1	..	..	..	1	..	..	1	7
9	1	..	..	1	..	..	..	..	..	..	..	..	2
10	4	..	..	2	..	..	..	..	2	..	..	..	8
11	3	..	..	..	..	..	..	..	1	..	..	..	4
12	2	1	1	4	..	..	..	..	..	..	..	..	8
13	1	..	..	1	..	..	..	..	..	..	..	..	2
14	6	..	..	1	..	..	..	..	..	..	..	..	7
15	1	..	..	..	1	..	..	..	..	..	..	..	2
Total number	28	2	2	18	2	1	5	1	12	1	2	2	72

was from 7 to 14 millivolts and that for the tibialis from 2 to 11 millivolts. In most cases we compared the amplitude of the reinnervated muscle with that for the corresponding normal muscle in the opposite limb and noted no amplitudes above 3 millivolts, except for 6 millivolts in 1 case. It is interesting to note that in normal muscles the higher potentials are also recorded in small distal muscles. The large spikes varied in frequency from 8 to 40 per second. Frequencies were correlated with strength of contraction and showed the same variation as do normal motor units. These spikes appeared with onset of contraction but in some cases fatigued easily, being difficult to sustain (fig. 6). On occasion, however, we have noted their persistence through a contraction of maximum effort for as long as one minute. The appearance of these spikes is not related to over-all strength of contraction. They appear whether the contraction is weak or strong. The following experiment demonstrates this point to some extent.

It is difficult to relearn the fine, intricate, isolated movements of the small muscles of the hand after regeneration of the median or ulnar nerves. However, these muscles can be used in associated or gross movements. For example, after regeneration of the ulnar nerve the isolated movement of abduction of the fifth finger, when the abductor digiti quinti is used, is difficult even with a great effort and results in in a weak contraction. When the same muscle is used in an associated movement, as in making a fist, a good contraction results. The two records (fig. 7) were made from the same lead in the abductor digiti quinti, the upper one while the subject was making a fist, and the lower on his attempting abduction of the fifth digit. While the patient was making a fist, a number of units of the large spike type were active, as well as some with small potentials (*A*), whereas in the isolated motion only one large spike, firing at about one-third the average frequency shown in *A*, was recorded in *B*. This corresponds to the phenomenon observed in normal muscles, in which strength of contraction is the product of the number of active units, as well as of their frequency. The

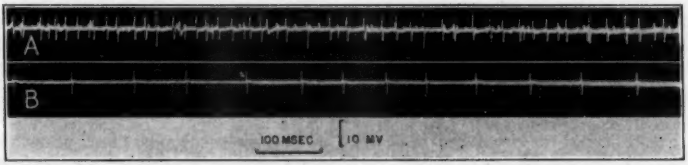

Fig. 7.—Records from the same lead in the abductor digiti quinti muscle four years after suture of the ulnar nerve, taken *(A)* while making a fist and *(B)* while spreading the fingers.

only difference here is that the weaker contraction is accompanied with activity of one unit of extraordinarily large potential.

We have found it advantageous in dealing with reinnervated muscles to have the patient perform a variety of motions with the muscle under investigation. In so doing, one not only is able to vary the intensity of a contraction, but can study the muscle in relation to other muscles in the same nerve distribution, as well as in its relation to antagonist muscle groups.

Figure 8 shows a record made from the gastrocnemius in a case of suture of the sciatic nerve. In *A*, taken while the patient was performing plantar flexion of the foot a number of spikes are noted, including one of the large spike variety. *B* was recorded from the same lead with the patient performing the opposite motion of dorsiflexion of the foot: Here a single large spike is seen. The occurrence of activity with an antagonistic movement suggests cross innervation of this muscle, with fibers normally destined for the tibialis anterior taking abnormal channels

and ending in the gastrocnemius. Watkins, Brazier and Schwab [8] noted a similar response in a reinnervated gastrocnemius muscle, which they termed "disruption of reciprocal innervation."

The muscles in which large spike potentials were obtained showed varied strengths of contraction on manual testing. These ranged from ability to move the part only without resistance to 90 per cent of normal power. Chronaxias of the muscles were all within the normal range, indicating that variation in strength was not a result of lack of reinnervation but was based on loss of muscle mass. In addition, an attempt was made to estimate the amount of muscle mass by comparing the strength of contraction of the affected muscle with the strength of contraction of normal muscle when its nerve was stimulated with supramaximal shock. In muscles in which large spikes occurred when tested in this way, from 20 to 80 per cent of muscle mass remained. We noted no spontaneous activity in these muscles at rest and were unable to demonstrate polyphasic units of the variety described by Weddell, Feinstein and Pattle. The large spike potentials were obtained in all cases, though they were not always available from the initial position of the needle. However, when the needle was moved so that the shortest

Fig. 8.—Records from the same lead in the gastrocnemius three years after suture of the sciatic nerve, taken *(A)* during plantar flexion of the foot and *(B)* during dorsiflexion of the foot.

duration of a smooth-contoured, diphasic potential was obtained, this potential was persistently of the large amplitudes noted.

Since the large potentials appeared to be characteristic of this type of muscle and their range of amplitudes was out of all proportion to that seen in normal muscle, we considered several explanations of these findings. Synchronization of motor unit activity has been described by a number of authors in conditions involving the lower motor neuron. Buchthal and Clemmesen [9] demonstrated synchronized motor units, which they termed single oscillations occurring in muscles having "neurogenic" atrophy. The potentials they described did not maintain their integrity of form or amplitude throughout a contraction and had a time interval two to three times as long as normal potentials. If these potentials are the result of synchronization of motor units, they differ greatly

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from the potentials in reinnervated muscles described in this study. The potentials we are concerned with maintain their smooth-contoured, diphasic form and their consistency of amplitude, except for slight variations due to movement of the needle during contraction; and their duration is within the range of normal units.

Denny-Brown [10] reported a large spike potential occurring in any disorder accompanied with reduction in number of active motor units and wasting of the muscle. These potentials he termed "contraction fasciculations," and he described the units as being innervated in the exercise of considerable effort and having an amplitude on occasion of over 1 millivolt. He regarded this phenomenon as the result of the uncovering of a normal large unit by the disappearance of many smaller units. The spikes we found in reinnervated muscles may be similar, since they are large and since a variable degree of atrophy occurs after nerve suture. However, the potentials derived from these muscles occur regardless of strength of contraction, and may appear against a background of strong electrical activity. The latter feature seems to rule out reduction in motor units or shunting effects as the cause of the large potentials.

A number of anatomic features of reinnervated muscle were elaborated on by Gutmann and Young.[11] These authors showed that in the process of nerve regeneration abnormal anatomic patterns occur relating the axon to the muscle fiber in a new fashion. Nerve fibers escape from the normal channels and form new end plates. In so doing, one nerve fiber may innervate several end plates in series. In consequence, a reconstruction of motor units takes place. Similar observations were made by Van Harreveld [12] in muscles which had been denervated and in which regrowth of the normal nerve supply had been inhibited. From his studies with this type of muscle, he concluded that increase in the branching of end ramifications of adjacent motor fibers of normal muscle was responsible for the phenomenon of spontaneous reinnervation in denervated muscles. Van Harreveld termed this "growth of the motor units" and recorded action potentials ten times the normal size from such muscles. Eccles and Sherrington,[13] Clark,[14] Hoefer and Put-

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11. Gutmann, E., and Young, J. Z.: The Re-Innervation of Muscle After Various Periods of Atrophy, J. Anat. **78**:15-43, 1944.

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nam,[15] Seyffarth,[16] Weddell, Feinstein and Pattle[2] and others have shown that motor units differ in size and that the discharge voltage is a direct expression of the anatomic size of the unit. Thus, units with a few fibers give small potentials, and those with many fibers, larger potentials. To draw the obvious conclusion concerning the origin of the large spike, one needs only to establish the fact that one is dealing with a single motor unit. We have found no evidence to contradict Adrian and Bronk's criteria that action potentials may be assumed to arise from a single motor unit when they are of the same shape and form part of a regular rhythmic series, with relatively uniform amplitude, in the same contraction. It appears, then, that the large spike potentials of reinnervated muscles are the result of the reconstitution of the motor units into units of an increased number of fibers.

SUMMARY

A study of the action potentials in 76 cases of reinnervated muscles three to five years after suture of the peripheral nerve is presented.

Two outstanding electromyographic patterns were recorded in these muscles: (*a*) a combination of spontaneous action potentials and small motor unit discharges on effort, and (*b*) large spike potentials, ranging in amplitude from 3 to 15 millivolts, occurring with volitional contraction and having the characteristics of motor unit discharges.

A correlation of the electromyographic changes and the anatomic characteristics of reinnervated muscle is suggested, namely, that the motor units responsible for the large potentials contain a larger than normal number of muscle fibers.

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PHANTOM LIMB PAIN AND CENTRAL PAIN

Relief by Ablation of a Portion of Posterior Central Cerebral Convolution

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PHANTOM limb pain was first described by Ambroise Paré [1] in 1551, and many theories have since been advanced to explain it. The present study was made with the thought of developing a form of therapy for this extremely painful entity. A review of the literature revealed an unusual variation in types of therapy. Among such procedures are removal or resection of a painful neuroma at the stump, further reamputation, sympathectomy, ganglionectomy, chordotomy, posterior rhizotomy, leukotomy and, in some cases, focal ablation of the cortex in the posterior central convolution.

In 1871 Weir Mitchell [2] published his work and gave the term by which this condition is known—phantom limb pain. He stated that a person with this condition is haunted, as it were, by a constant or an inconstant fractional phantom of so much of himself as has been lopped away. He was the first to faradize the track of the nerves in or above the stump. As a result of this stimulation, the patient felt as though he had the limb or hand or foot that had been amputated. Weir Mitchell stated the belief that this phenomenon was due to irritation of sensory trunks, which occasioned impressions of muscular motion in the sensorium. He found that 95 per cent of patients experience phantom limb after amputation, albeit no pain.

Henderson and Smyth's [3] study of 300 cases revealed that phantom limb was a natural, and almost universal, sequel to amputation. They reported three kinds of sensory phenomena: (1) mild tingling, which forms the basic part of the phantom in nearly every case and probably

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Read at the Fourth International Neurological Congress, Paris, France, Sept. 5, 1949.

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1. Paré, A.: La methode de curer les combustions principalement faictes par la pouldre à canon, Paris, Iean de Brie, 1551.

2. Mitchell, S. W.: Phantom Limbs, Lippincott's Mag. **8**:563-569, 1871.

3. Henderson, W. R., and Smyth, G. E.: Phantom Limbs, J. Neurol., Neurosurg. & Psychiat. **11**:88-112, 1948.

arises in the cerebral cortex; (2) stronger, pins and needles, sensations, induced momentarily by touching a neuroma in the stump, and (3), occasionally, superimposed sensations, which may be disagreeable and painful and probably have a psychogenic basis. The phantom limb pain may develop soon after the amputation or several weeks later. In many instances the pain vanishes without any treatment. Some authors have attempted to explain the phantom on the basis of stimuli arising in the severed nerve ends in the stump. Head [4] said that there is a body scheme which is formed from the confluence of all the kinesthetic and tactile sensations. Because of the greater activity of the ends of the extremities, more stimuli are received from them and they become the most clearly felt part of the body scheme. Pflügge [5] stated that the phantom limb pain is the result of an attempt to restore the psychic body scheme. It is believed that it is a form of narcissism; that is, no one dreams of himself as having lost a part. Pflügge reported a case of a soldier with an amputated forearm who experienced symptoms of phantom limb ten days after the accident. The patient felt the forearm pressing against his chest. A neuroma was resected, with no relief. Injection into the stellate ganglion brought temporary relief. Psychoanalytic therapy did not help, and manipulation of the stump was a failure so far as relief was concerned.

Pitres [6] found that 97 per cent of amputees had phantom limb pain, while Souques and Poisot [7] stated that injection of cocaine around the terminal scar caused a constant, but short-lived, disappearance of all hallucinations suffered by the patients. Dusser de Barenne,[8] while working on sensory localization in the cerebral cortex, concluded that superficial sensibilities are represented bilaterally in both the thalamus and the cerebral cortex. Flothow,[9] Spurling [10] and White and Smithwick [11] reported cases of pain relieved by sympathetic ganglionectomy.

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11. White, J. C., and Smithwick, R. H.: Painful Disorders of Extremities, in The Autonomic Nervous System, New York, The Macmillan Company, 1941, pp. 229-236.

Bychowsky and Eidinow [12] demonstrated bilateral sensory disturbances in patients with a unilateral cerebral lesion. Förster [13] stated that all sensory modalities may be affected after cortical ablation of the posterior central convolutions.

Leriche [14] found that 98 per cent of all amputees had phantom limb pain. He produced sympathetic ganglion interruption surgically or by infiltration anesthesia, with some success; but the effects lasted only a few weeks. Walker,[15] in 1939, stated the opinion that when the cortex of the posterior central convolution is removed on one side and the patient feels pain the phenomenon is due to a pathway to the ipsilateral thalamus and the cortex of the normal hemisphere. This, he stated, means that there is bilateral representation of certain modalities of sensation. He stated further that there is always retention of normal pinprick sensation in the face after hemispherectomy. Walker,[16] again in 1942, stated that there are three levels at which pain sensations may be integrated: (1) The cerebral cortex. Pain impulses to this region are appreciated as pain; an illustration is pinprick. Removal of the cortical area should relieve phantom limb pain. (2) The thalamus. Pain fibers are gathered in the posterior ventral nucleus and pass to the posterior central convolution of the cerebral cortex. (3) The tectum mesencephali. This is the third, and lowest, level for integration of pain. This path is probably not very active in man.

Lhermitte and Puech [17] reported a case of phantom limb pain that was not relieved by resection of a neuroma, infiltration of the sympathetic nerve chain, posterior myelotomy and, finally, resection of the parietal lobe. Pisetsky [18] described a case of phantom limb pain relieved by seven electric shock treatments. Falconer and Lindsay [19] reported 2 cases of phantom limb pain which was relieved permanently by chordotomy in the high cervical region. Browder and Gallagher,[20] reporting

12. Bychowsky, G., and Eidinow, M.: Doppelseitige Sensibilitätsstörungen bei einseitigen Gehirnherden, Nervenartz **7**:498-506, 1934.

13. Förster, O.: Ueber Das Phantomglied, Med. Klin. **27**:497-500, 1931; Der Schmerz und seine operative Bekämpfung., Nova Acta Leop. Carol. **3**:1-60, 1935.

14. Leriche, R.: La chirurgie de la douleur, Paris, Masson & Cie, 1937.

15. Walker, A. E.: The Origin, Course and Terminations of the Secondary Pathways of the Trigeminal Nerve in Primates, J. Comp. Neurol. **71**:59-89, 1939.

16. Walker, A. E.: Central Representation of Pain, A. Research. Nerv. & Ment. Dis., Proc. (1942), **23**:63-85, 1943.

17. Lhermitte, J., and Puech, P.: L'algo-hallucinose des amputés, Rev. neurol. **78**:33-35, 1946.

18. Pisetsky, J. E.: Disappearance of Painful Phantom Limbs After Electric Shock Treatment, Am. J. Psychiat. **102**:599-601, 1946.

19. Falconer, M. A., and Lindsay, J. S. B.: Painful Phantom Limb Treated by High Cervical Chordotomy, Brit. J. Surg. **33**:301-306, 1946.

20. Browder, J., and Gallagher, J. P.: Surgical Treatment of Painful Phantom Limb, New York State J. Med. **46**:2403-2405, 1946.

on surgical treatment of painful phantom limb, stated that in their case the pain was relieved by chordotomy. Pool [21] said that phantom limb pain occurs in about 6 per cent of all amputees. In a case with a burning, cramping pain resembling causalgia he produced relief by sympathectomy. In another case with the sensation that the phantom limb was clamped in a tight fixed position relief resulted from posterior chordotomy. In another case posterior chordotomy and sympathectomy failed to relieve pain.

White [22] stated that there is promising evidence that phantom limb sensation can be cured by resection of the sensory cortex. He expressed the opinion that other procedures which had been found ineffective should never be tried again. Horrax [23] reported 4 cases of intractable pain relieved by cortical excision of the posterior central convolution. Ewalt and Randall [24] reported on 404 cases in a series of 2,284 amputees, in which detailed psychiatric studies had been made. They found evidence of phantom limb complaints in all the 404 cases. They also found considerable evidence of psychopathologic disorders. Rorschach profiling revealed free floating anxiety, confusion and great concern for future adjustment. They stated that in some stable persons phantom limb sensations gradually disappeared, whereas in patients who were emotionally disturbed phantom limb pain remained or recurred frequently in times of emotional distress, regardless of the treatment given. Echols and Colclough [25] reported a case in which a painful phantom foot was abolished by surgical excision of the corresponding part of the posterior central convolution on the opposite side. Their patient had had four other types of therapy before the cortical ablation—sympathectomy, second amputation above the original one, resection of the neuroma of the sciatic nerve and, finally, spinal anesthesia—none of which gave relief

Walker,[26] in a personal communication on Dec. 9, 1948, stated that the arm and leg have relatively little ipsilateral representation for pain. The face, however, has bilateral representation for pain. He further remarked that it is true that in rare cases an extremity is represented ipsilaterally, probably owing to failure of the pathways to cross. He

21. Pool, J. L.: Posterior Chordotomy for Relief of Phantom Limb Pain. Ann. Surg. **124**:386-391, 1946.

22. White, J. C.: Painful Injuries of Nerves and Their Surgical Treatment. Am. J. Surg. **72**:468-488 (Sept.) 1946.

23. Horrax, G.: Experiences with Cortical Excisions for Relief of Intractable Pain in Extremities, Surgery **20**:593-602, 1946.

24. Ewalt, J. R.; Randall, G. C., and Morris, H. D.: Phantom Limb. Psychosom. Med. **9**:118-123 (March) 1947.

25. Echols, D. H., and Colclough, J. A.: Abolition of Painful Phantom Foot by Resection of Sensory Cortex, J. A. M. A. **134**:1476-1477 (Aug. 23) 1947.

26. Walker, A. E.: Personal communication to the author.

cited a case of French and Peyton in which ipsilateral sensory loss followed chordotomy. He also said that the main reason for failure of ablation of a posterior central convolution to relieve phantom limb pain is probably the fact that this convolution is only a small part of the sensory representation of the extremity. There is a rather diffuse representation in the posterior parietal lobules for pain and for other sensory modalities (that is, kinesthetic and tactile), considered by the patient as uncomfortable and distressing. Walker stated the belief that a great many cases of phantom limb pain are the result of a combination of circumstances, one being an organic factor and another a psychogenic factor. The prefrontal lobotomy relieves the psychogenic factor in some cases but leaves undisturbed the organic factors. On the other hand, he stated, chordotomy affects only the organic factor in phantom limb pain. Walker stated that chordotomy is the best operation on the spinal cord for relief of phantom limb pain.

Le Beau, Bouvet and Rosier [27] stated that they had treated 10 patients with irreducible pain by topectomy. By this term they meant bilateral fractional resection of cortical areas 9 and 10 of Brodmann, and occasionally area 46. They removed not more than 13 to 14 Gm. of substance. They stated the opinion that areas 9 and 10 are connected with the medial thalamic nuclei and that area 9 is also connected with the nuclei of the septum of the preoptic region. Watts and Freeman [28] reported prefrontal lobotomy as being successful in the treatment of intractable pain of carcinoma, tabes, radiculitis, causalgia, phantom limb and the thalamic syndrome. After this operation the patient can still feel pain, but he is not concerned about it.

Riddoch [29] stated that nearly one-half the patients with amputations, both traumatic or surgical, have painful phantom limb and that it appears oftener with amputation of the upper extremity than with that of the lower. The patient may have paroxysms of pain resulting from stimulation of nerve endings in the stump. Yawning, defecation, micturition, worrying and fatigue may initiate the paroxysms of pain. When pain has been present for some time prior to the amputation, a painful phantom limb can almost certainly be predicted. Riddoch stated that a tender neuroma is usually associated with painful phantom limb. He asserted that destruction of cortical sensory mechanism in the parietal lobe, which is concerned with the development of postural and surface models and with the recognition of change, causes immediate abolition of the phan-

27. Le Beau, J.; Bouvet, M., and Rosier, M.: Traitement des douleurs irreductibles par la topectomie, Semaine des hôp. Paris **24**:1946-1952, 1948.

28. Watts, J. W., and Freeman, W.: Development of Prefrontal Lobotomy in the Treatment of Intolerable Pain, South. Med. & Surg. **110**:1-3 (Jan.) 1948.

29. Riddoch, G.: Phantom Limbs and Body Shape, Brain **64**:197-222 (Dec.) 1941.

tom limb. De Gutiérrez-Mahoney [30] stated that almost 100 per cent of his patients had painful phantom limb. It was, however, disabling in very few. In his cases the phantom had an organic basis. This painful condition can be abolished by interruption of the sensory chain leading to consciousness. He stated the belief that it is easier and simpler to interrupt the chain by removal of the corresponding part of the posterior central convolution.

Herrmann and Gibbs [31] studied the incidence of phantom limb pain in a series of 120 patients who had amputation of an extremity. They found that of 4 patients who had a severe trauma before amputation, 1 (25 per cent) had phantom limb pain. Of the entire series of 120, only 5.8 per cent had phantom limb pain. The analysis of the clinical data presented on this series indicates that the treatment of the large nerves at the time of amputation is of considerable importance in preventing occurrence of phantom limb pain. The authors recommend placing a tight ligature about the uninjured large nerve trunk at a point 1 inch (2.5 cm.) above the level of amputation. This constitutes a simple and physiologic method of preventing the regeneration of the axons from the cut end of the nerve. They stated the opinion that irritation of the centrally conducting axons by neuromas, local inflammatory changes and abnormal scar tissue formation about the end of the nerves may give rise to intractable pain in the phantom limb after amputation.

Magoun,[32] of Northwestern University Medical School, stated that the posterior central convolution of the brain is one of receptive centers for the consciousness of pain, such as that from pinprick. He expressed the belief that the parietal cortex also contains areas for the conscious appreciation of pain. Magoun stated that ablation of a specific area in the posterior central convolution should relieve pain in a specific area on the opposite side of the body.

REPORT OF CASES

Case 1.—W. M., a man aged 27, was admitted to the neurosurgical service at the Veterans Administration Hospital at Hines, Ill., on Jan. 17, 1948. He had been transferred from another hospital in Texas. The diagnosis on admission was phantom limb pain (left hand and forearm). The family history was of no importance. The patient had been well until June 5, 1944, when, while serving in the Army as a paratrooper in France, he received a pistol shot wound in the right forearm and a penetrating gunshot wound in the abdomen. He gave himself first aid treatment. On June 10, 1944 he had a traumatic amputation of his left forearm from a shell fragment wound. Ever since he had been conscious of a phan-

30. de Gutiérrez-Mahoney, C. G.: The Treatment of Painful Phantom Limb by Removal of Post-Central Cortex, J. Neurosurg. **1**:156-162, 1944.

31. Herrmann, L. G., and Gibbs, E. W.: Phantom Limb Pain: Its Relation to Treatment of Large Nerves at Time of Amputation, Am. J. Surg. **67**:168-180, 1945.

32. Magoun, H. W.: Personal conference with the author.

tom hand. The hand was painful, and he felt that the fingers of the phantom hand were forcibly flexed on the thumb. Furthermore, his phantom hand felt as though it were attached to the stump of the left forearm. He also stated that the palm of the phantom left hand felt as if it were raw. At the time of examination, the pain ran from the hand up into the left forearm and arm into the shoulder. It was not constant and might last for a few minutes or for ten or twelve hours. In addition to this sharp phantom pain, he had a dull ache in the left arm and shoulder, as well as a clenching sensation in the phantom hand. Since 1945 the patient had had three operations for removal of a painful neuroma. These gave him only temporary relief, the pain always recurring. On one occasion a screw was placed between the radius and the ulna in the stump, on the assumption that part of his pain was due to hypermobility of these bones. This operation failed. He then received intravenous injections of procaine hydrochloride and block of the brachial plexus, sympathetic chain and ganglia, all these procedures failing miserably.

On Feb. 16, 1948 Dr. John Martin did a craniotomy with osteoplastic flap on the right side and made the following report: "What I took to be a vein of the rolandic fissure ran through a point from below upward approximately at the junction of the anterior and the middle third of the area of exposure of the brain. The patient was fully alert and did not complain of anything but inability to get sufficient air, although oxygen was being blown into his face. When I placed the stimulator lightly in front of the vein, he had a generalized convulsion and lost consciousness. By means of cold dissection and suction I resected the gray matter of the loop of gyrus which seemed to be the sensory cortex for the hand and forearm. The circulation was not disturbed except at the excised area, which was approximately 1 cm. wide, 1 cm. deep and a little over 2 cm. long. He had no pain anywhere and no sensations or distress in the stump of the left upper extremity. He was discharged on March 10. Four weeks after his discharge he was again conscious of his phantom hand, but it was not painful. He has remained free from pain since the operation, a period of ten months."

Case 2.—W. T., a man aged 28, was admitted to the Wesley Memorial Hospital on Feb. 14, 1948. In October 1944 he was in a motorcycle accident and sustained a compound fracture of the left femur with subsequent osteomyelitis. In May 1945 the left foot, the left leg and the lower portion of the left thigh were amputated. Two weeks later there developed sharp, flashing, cutting pain in the heel of the phantom limb. Any movement of the stump resulted in exacerbations of the phantom limb pain. He could not wear his artificial leg because it also brought on pain. At the time of examination the pain in the phantom limb was constant. Neurologic examination failed to show any objective evidence of organic disease of the central nervous system. The patient obtained some relief from drinking alcohol. Infiltration of the sciatic nerve with procaine did not relieve the phantom limb pain.

On Feb. 17, 1948 Dr. John Martin did a craniotomy with osteoplastic flap on the right side, with local anesthesia. With alternating current from the usual stimulator, he found the gyrus back of the large vein, which appeared to be the vein of the rolandic area. Stimulation exactly at the midline, at the turn of the hemisphere, produced exquisite pain and tingling in the phantom foot and leg as high as the stump. The area involved seemed to be 1.5 cm. long and 1 cm. wide and to be well deprived of blood vessels. With spatula and fine suction tip, that portion of the gyrus was removed up to the walls of the neighboring gyri. When this excision was completed, the patient said that he did not feel the phan-

tom leg, either pain or sensation. He did feel numbness about the stump. Since the operation, the patient has not had any pain or sensation of phantom limb. At the time of this report, eleven months after the craniotomy, he is entirely well.

Case 3.—M. L., a woman aged 58, had been admitted to the Wesley Memorial Hospital on eight occasions. The patient had both central and phantom limb pain. Her first admission was on Sept. 4, 1943, when she was found to have paralysis of the right arm and leg, associated with motor aphasia, high blood pressure and sclerosis of the cerebral vessels. The blood pressure at that time was 200 systolic and 108 diastolic. The family history was of no importance. The patient's husband stated that in 1940, three years prior to her present trouble, she became blind in the right eye. The blindness came on suddenly, and vision had improved, so that at the time of the first examination vision was 50 per cent normal. The patient had had severe headaches in the previous ten years or more. In 1943 she showed paresis of the right side of the face of central type and, on the right side, flaccid hemiplegia, absence of both upper and lower abdominal skin reflexes, sustained ankle clonus, and Babinski and Chaddock signs. Her condition remained the same on all her later admissions except that her right upper and lower extremities had become stronger. On her second admission the right hand was swollen and painful. Her third admission was for the treatment of acute cystitis. On her fourth and fifth admissions she had complained of severe pain in the right hand and forearm. This pain was acute and felt as though some one were stabbing her with a sharp needle. Between her fourth and fifth admissions a chordotomy was done in the cervical region, which did not relieve her pain. Because of the severe pain in the right hand and forearm, the patient had the right arm amputated at the shoulder at another hospital, after her seventh discharge from the Wesley Memorial Hospital. On Sept. 10, 1947 the patient was admitted to Wesley Memorial Hospital for the eighth time. I saw the patient for the first time September 12. At that time there was a history of attempted suicide on two previous occasions, and at the time of that admission she had tried to kill herself by slashing her right ankle. She complained of constant excruciating and stabbing pain in the phantom arm. She stated she felt as though her right hand were touching hundreds of sharp-pointed pins. Nothing relieved this pain. The lower part of her face and the platysma muscle were paretic on the right side. The retina showed conspicuous sclerosis with no hemorrhages or exudations. The upper and lower abdominal skin reflexes were absent bilaterally. The right lower extremity was markedly paretic and showed brisk knee and ankle reflexes. There was an unsustained ankle clonus on the right with Babinski, Gordon, Oppenheim and Chaddock signs on the same side. Pinprick sensation was not appreciated in the right shoulder, the right side of the chest and abdomen and the right lower extremity as well as it was on the corresponding structures on the left side. The blood pressure at this time was 230 systolic and 110 diastolic. I felt that this phantom limb pain was central and real, and not imaginary or psychogenic. Focal ablation of the corresponding area in the left posterior central convolution was recommended. On Sept. 28, 1947 Dr. John Martin extirpated the area. He reported that the gyrus was sucked out from the posterior border of the free rolandic gyrus on the left side to another clearcut gyrus, obviously in the sensory area. After this procedure the patient had a convulsion, became unconscious and had a truly stormy convalescence. When she awakened, she had motor aphasia. When she was discharged, on October 9, her aphasia had become much improved, and she had no phantom limb pain. Fourteen months later the patient continued to be free from phantom limb pain.

COMMENT

Why and when does phantom limb pain occur? It is well known that phantom limb pain never occurs in patients who have had a congenital amputation, an amputation in infancy, amputation of a frozen limb or amputation in which the nerve or nerves of the involved extremity are resected or cut at a considerable distance above the stump. Phantom limb with or without pain may or may not occur with every type of amputation except those just mentioned. In a considerable number of amputations the symptoms are present for a short period and then gradually disappear. Certainly, in emotionally and nervously unstable persons various symptoms can and do occur. These should be classified as psychogenic, and this paper is not concerned with their treatment. In a certain number of cases the phantom limb symptoms are entirely organic in origin, and it is in these cases that I am particularly interested in developing an efficient surgical procedure for relief of the pain. The incidence of such complaints, I believe, occur oftener and more frequently in the older patient. This is true because the older patient has developed a picture in his or her consciousness which is deeper seated in the memory than in the younger person. Phantom limb pain occurs more frequently in the upper extremity than in the lower. Ambroise Paré said that phantom limb pain was due to the retraction of divided nerves. Weir Mitchell said it was due to peripheral irritation in the stump. For three and a half centuries evidence was accumulated which pointed clearly to the peripheral nerve stump as producing this bizarre group of symptoms. The conclusion reached was that stimuli originating at the periphery of the amputated nerves transmit these impulses by all possible pathways to registration in consciousness. Certainly, in order that the patient may have such symptoms, there must be three active parts, namely; divided and exposed nerves in the stump, patent nerve pathways from the stump and a mature sensory cortex and consciousness to receive these impulses. It should be obvious, therefore, that in order to remove such signs one would have to sever every nerve and its pathways from the stump to the portion of the sensory cortex concerned with consciousness. This, however, would require considerable time and tremendous risk. Assuming that the symptoms are in the consciousness of the sensory cortex, it seems that relief of such symptoms could easily be carried out by subpial resection of the area in the posterior central convolution for the extremity involved. This procedure must, of course, be limited to patients who have symptoms of the organic type of phantom limb only. These symptoms may be of various types and are as follows: undue warmth; itching or distress in the phantom limb; intermittent or continuous severe burning pain; deep agonizing, torturing sensations; piercing, cramping or cutting pains, and various types of throbbing and stabbing sensations. The various other types of sensory

disturbances complained of by the patient, such as kinesthetic and tactile sensations, defects in the body scheme and postural abnormalities, are not be considered as indications for surgical relief and therefore are not to be treated by resection of the corresponding posterior central convolution. In my opinion, such a procedure would fail to relieve these symptoms. Posterior chordotomy or resection of the posterior columns and horns in the cervical portion of the spinal cord is the procedure of choice for such complaints.

Without his being dogmatic, the neurosurgeon should not carry out any procedure for relief of phantom limb or central pain unless he is sure that the pain is of organic nature. When he feels that the patient's pain is of this type, he should do a subpial resection of the corresponding area in the posterior central convolution. By doing this, and affording relief, he may prevent addiction to morphine or other drugs, acute alcoholic debauchery or suicide. If the aforementioned operation is considered effective, no other surgical procedures should be carried out. The surgeon should be certain that all the nerves are resected high above the stump at every amputation.

SUMMARY

Three cases of phantom limb pain of organic origin, 1 (case 3) of central pain, are reported. In all 3 permanent relief was effected by subpial resection of a corresponding area in the posterior central convolution. If this is the operation of choice, and I believe that it is, it is strongly urged that no patient be made to undergo any other type of surgical procedure, because of the risk of failure, with the development of many complications.

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MAGNESIUM INTOXICATION

Absorption from the Intact Gastrointestinal Tract

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MAGNESIUM sulfate U. S. P. (Epsom salt) is used in medicine chiefly for two effects. When given parenterally in small doses, it is an effective cerebral depressant, and therefore useful in the control of convulsions. When introduced into the gastrointestinal tract in hypertonic solution it is considered to be poorly absorbed, and therefore useful for its osmotic effect. In drawing water from the body, it accomplishes both dehydration and diarrhea. In amounts of 15 to 20 Gm. it is often given by mouth as a laxative, and in approximately the same amounts it is one of the constituents of the familiar "magnesium sulfate, glycerin and water" enema.

This report is chiefly concerned with the widespread practice of administering large amounts of magnesium sulfate by slow drip per rectum to induce dehydration in the management of increased intracranial pressure and cerebral edema. It has usually been assumed that this procedure is harmless because magnesium sulfate is poorly absorbed from the rectum, and that therefore it is a useful preoperative procedure for patients with brain tumor and increased intracranial pressure.[1] Recent experience with 2 patients has led to a reevaluation of the pharmacology of magnesium sulfate.

In 1909 Fraser[2] reviewed the literature from 1841 to 1909 on the toxicity of Epsom salt and found evidence of poisoning in 7 cases, with 5 fatalities. All the patients had taken the salt by mouth, and depression of the central nervous system was the most serious toxic effect. Fraser suggested that the toxicity might be based on a central effect, from

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1. Fay, T.: The Administration of Hypertonic Salt Solutions for the Relief of Intracranial Pressure, J. A. M. A. **80**:1445 (May 19) 1923; Comparative Values of Magnesium Sulphate and Sodium Chloride for Relief of Intracranial Tension, ibid. **82**:766 (March 8) 1924.

2. Fraser, C.: Epsom Salts as a Poison, with a Record of a Case of Unusual Symptoms Due to This Drug, Lancet **1**:1174, 1909.

absorption of the drug. In the same year Mendel and Benedict [3] reported on the excretion of magnesium salts. When the salts were given parenterally to animals, 80 per cent could be recovered from the urine within forty-eight hours. The role of the kidneys in excreting magnesium salts has been repeatedly emphasized, and in 1934 Hirschfelder [4] pointed out that in persons with renal damage oral administration of magnesium sulfate may be associated with elevation of the magnesium level of the plasma from a normal of 2 mg. to as high as 8 or 15 mg. per hundred cubic centimeters, with accompanying drowsiness and near coma. The same investigator produced renal damage in rabbits, and in these animals the administration of magnesium sulfate by mouth led to high magnesium levels in the blood. Values of 17 mg. per hundred cubic centimeters or higher were associated with coma in the rabbits. It was pointed out that magnesium coma may be difficult to distinguish from uremic coma. Hirschfelder also gave 20 to 30 Gm. of magnesium sulfate by mouth to persons with normal renal function and obtained "insignificant" increases of the plasma magnesium (0.2 to 0.4 mg. per hundred cubic centimeters), but he recovered 40 to 44 per cent of the ingested magnesium in the urine within twenty-four hours, thus demonstrating that a large amount had been absorbed. The magnesium content of the stools was not measured.

Hoff,[5] in 1939, studied the toxic effects of magnesium sulfate in dogs. In isotonic solution, the salt was injected intravenously, and levels of serum magnesium were correlated with observations on blood pressure, respiration and general behavior. A decline in blood pressure was noted with a level of 6 mg. per hundred cubic centimeters, or even below, and thereafter evidence of increasing cerebral depression. A level of 18 to 20 mg. per hundred cubic centimeters was associated with respiratory arrest, and when the dogs were kept alive with artificial respiration, a level of 32 to 46 mg., with cardiac arrest. Neuwirth and Wallace,[6] exploring the possibilities of magnesium as an aid in anesthesia, reported that in healthy dogs a serum magnesium level of 5 mg. per hundred cubic centimeters was correlated with definite evidence of cerebral depression, and one of 19 to 23 mg. per hundred cubic centimeters, with complete anesthesia. These investigators also reported that the rectal administra-

3. Mendel, L. B., and Benedict, S. R.: The Paths of Excretion for Inorganic Compounds: IV. The Excretion of Magnesium, Am. J. Physiol. **25**:1, 1909.

4. Hirschfelder, A. D.: Clinical Manifestations of High and Low Plasma Magnesium: Dangers of Epsom Salt Purgation in Nephritis, J. A. M. A. **102**:1138 (April 7) 1934.

5. Hoff, H. E.; Winkler, A. H., and Smith, P. K.: Cardiovascular and Neuromuscular Changes Following Intravenous Injections of Magnesium Salts, Am. J. Physiol. **126**:537, 1939.

6. Neuwirth, I., and Wallace, G. B.: On Use of Magnesium as an Aid in Anesthesia, J. Pharmacol. & Exper. Therap. **35**:171 (Feb.) 1929.

tion of 14 Gm. of magnesium sulfate to healthy dogs, and of 8 Gm. to healthy human subjects, resulted in insignificant elevation of the serum magnesium. They did not give larger amounts by rectum.

In 1922 Rector,[7] also interested in the potentialities of magnesium sulfate in anesthesia, gave to each of 5 patients 210 cc. of a 25 per cent solution by rectum. In all he obtained significant elevations of the serum magnesium, the average value at one hour being about 10 mg. per hundred cubic centimeters and the level falling to normal in four hours. Unfortunately, no clinical observations were reported.

In 1943 Fawcett and Gens[8] described 2 cases in which signs of magnesium poisoning followed an enema of Epsom salt. In the first, that of an infant, the diagnosis was made on clinical signs, no samples of blood being studied. In the second, a woman aged 23 with a ureteral stone, who was otherwise healthy, and presumably had normal renal function, was given an enema containing about 25 Gm. of magnesium sulfate with glycerin; this was assumed to be retained in the rectum approximately two minutes. After thirty minutes she felt hot and thirsty. One hour and fifteen minutes after the enema, she was found unresponsive, with respiration entirely abdominal and with complete areflexia. Intravenous injection of calcium, the pharmacologic antidote for magnesium, was given, with a dramatic response, the patient regaining consciousness within a few minutes. Three hours after the enema had been administered, blood was drawn, and its serum magnesium value was 20.8 mg. per hundred cubic centimeters. This is the highest value we have found reported in a human subject. Fawcett and Gens concluded that the intact bowel of some persons exhibits a peculiar ability to absorb magnesium sulfate.

At the New York Hospital, one-half saturated solution of magnesium sulfate is often given to patients with increased intracranial pressure, in the amount of 300 cc. administered by slow Murphy drip per rectum, at a rate of 1 drop per second, so that the whole volume is administered over a period of three hours or longer. Three hundred cubic centimeters of such a solution contains 94.5 Gm. of magnesium sulfate U. S. P. At the beginning of the enema, the patient may be nearly comatose from the effects of the increased intracranial pressure, and, as the dehydrating effect of the procedure becomes manifest, the patient characteristically becomes more alert. Significant absorption of the salt from the rectum has not until recently been considered a dangerous possibility. However, that untoward sequelae may occur when high

7. Rector, J. M.: Synergistic Analgesia: Clinical Observations, Am. J. Surg. (Anesthesia supp.) **36**:114 (Oct.) 1922.

8. Fawcett, D. W., and Gens, J. P.: Magnesium Poisoning Following an Enema of Epsom Salt Solution, J. A. M. A. **123**:1028 (Dec. 18) 1943.

concentrations are used is demonstrated by the 2 protocols which follow. To each of the patients, a fully saturated solution of magnesium sulfate was given for the purpose of accelerating dehydration.

REPORT OF CASES

Case 1.—A white girl aged 18 was admitted to New York Hospital for the fourth time because of repeated convulsions of the left side. During her first admission, four and one-half years earlier, an unclassified glioma was removed from the right temporoparietal area, and after operation the tumor site was exposed to repeated roentgen treatments. Subsequent admissions were for the control of convulsions involving the left side, which usually diminished in number after large amounts of phenobarbital were administered. For about two months before her final admission, the patient had increased considerably her fluid intake, chiefly with milk and cola beverages. She became irregular in taking her prescribed doses of phenobarbital. Two weeks prior to admission numbness of the left hand and right-sided headache were noted. The day before admission she began to have convulsions of the left side, which continued despite anticonvulsant medication. Physical examination revealed no definite change from that described on her previous admission, two years earlier. The findings included a bony defect in the right temporoparietal region, normal eyegrounds, weakness of the left side, pathologic reflexes and absence of the abdominal reflexes. The patient had frequent convulsions on the left side and was regarded as being in status epilepticus. At first she was given sodium phenobarbital subcutaneously, 0.13 Gm. after each convulsion, but this was reduced to 0.065 Gm. on the second day. The frequency of seizures was diminishing until the third night in the hospital, when she had several of long duration. Because of the history of increased fluid intake preceding the present series of seizures, it was considered that cerebral edema might be a factor. It was decided therefore to reduce the edema by a dehydrating procedure. Accordingly, 300 cc. of saturated solution of magnesium sulfate (189 Gm. of the salt) was administered per rectum, by slow Murphy drip, over a period of three hours. At the beginning of administration of the enema, the patient was listless, a state which was attributed to the barbiturates given during the preceding three days. One hour later the patient became restless and complained of local rectal irritation. At two and one-half hours her nurse noted that she was "very drowsy, but restless at intervals." At three hours, just as the enema was completed, the patient turned herself over onto her abdomen. Ten minutes later it was noted that she was cyanotic, with shallow respirations. The patient was turned on her back, and artificial respiration was begun immediately, resulting in a decided improvement in color. Although the heart beat was not audible through the chest wall at this time, a weak radial pulse was felt. Caffeine and sodium benzoate U. S. P., 0.5 Gm., was given intramuscularly, without effect. After ten minutes of manual artificial respiration, pure oxygen was given by intratracheal tube, with use of intermittent positive pressure. The radial pulse was no longer palpable, and the patient was pronounced dead within one-half hour of the termination of the magnesium sulfate enema.

Postmortem examination revealed extensive cerebral atrophy and a surgical defect in the right cerebral cortex. Microscopic examination showed no evidence of tumor, and the changes were gliosis and vascular thickening in the area exposed to roentgen radiation. A review of the microscopic sections from the original tumor, removed at operation, led to the diagnosis either of neurospongioblastoma

or of glioblastoma multiforme. The kidneys were entirely normal, grossly and microscopically, and it is of importance that during life, the results of urinalyses were unremarkable. No formal studies of renal function had ever been made.

Within one hour post mortem, specimens of heart's blood and spinal fluid were obtained. Magnesium levels were determined according to the method of Denis.[9] The value for the serum was found to be 20.1 mg. per hundred cubic centimeters and that for the spinal fluid, 3.1 mg., per hundred cubic centimeters. The latter is normal, but the serum level corresponds to the toxic levels reported in the literature.

Case 2.—A white woman aged 42 was admitted for the second time to New York Hospital because of numbness, weakness and convulsive movements of the left arm and leg. On her previous admission, sixteen months earlier, a glioblastoma multiforme had been partially resected from the right frontoparietal area. On admission, she was mentally alert, but exhibited weakness and hyperactive reflexes on the left side of the body and bilateral papilledema. In preparation for head surgery, a slow drip of magnesium sulfate solution per rectum was administered. After 100 cc. had been given, the patient was flushed and drowsy. After 200 cc., she was extremely lethargic, responding only to repeated noxious stimulation. After 250 cc., and at the end of three hours, she was comatose, although the vital signs were unchanged; and the drip was discontinued. All the fluid had been retained, and difficulty was experienced in obtaining returns, even after several enemas of soapsuds. Fifty cubic centimeters of 50 per cent dextrose was given intravenously, with slight immediate effect. The patient gradually became less drowsy and returned to full consciousness about two or three hours after the magnesium sulfate enema had been discontinued. No samples of blood were obtained during the episode. Because this was the only loss of consciousness which the patient experienced during this phase of her illness, it seemed logical to attribute it to the cerebral depressant effect of magnesium absorbed from the rectum. Studies of the urine demonstrated normal renal function, including adequate concentration.

EXPERIMENTAL STUDY

Series 1.—In order to learn more about the rectal absorption of magnesium sulfate, and to correlate more accurately the serum level of magnesium with the clinical state of the subject, the following experiment was performed. Voluntary participation was obtained of 6 male subjects, all of whom had normal urine and none of whom was taking digitalis. None of the subjects was receiving sedative medication. All received hypertonic solution of magnesium sulfate per rectum by Murphy drip, at a rate of approximately 1 drop per second, and it was planned to give 300 cc. to each. Subjects A, B, C and D received a one-half saturated solution, and subjects E and F received a saturated solution. All were carefully observed for evidence of drowsiness and were repeatedly asked to report on sensations of heat or thirst. Blood was withdrawn at approximately hourly intervals.[10] Calcium gluconate was available for intravenous injection, should extreme drowiness appear.

9. Hawk, P. B.; Oser, B. L., and Summerson, W. H.: Practical Physiological Chemistry, ed. 12, Philadelphia, The Blakiston Company, 1947.

10. All the analyses for serum magnesium content were performed by Dr. Rees Pritchett.

Observation.—All 6 subjects experienced some degree of cramps of the lower part of the abdomen. In 3 of the subjects receiving one-half saturated solution, the rectal tube was out of the rectum some of the time, and it is certain that none of the 3 received the full 94 Gm. of magnesium sulfate. None of them exhibited symptoms or signs attributed to a central effect of magnesium. Subject A insisted on abandoning the experiment after 150 cc. of the enema had been given because of abdominal cramps. The serum magnesium level before the enema was 2.3 mg. per hundred cubic centimeters; at the time of discontinuation, 3.6 mg., and one hour later 2.8 mg. Subject B also had a control serum magnesium level of 2.3 mg. per hundred cubic centimeters, which rose to 3.9 mg. at two and one-half hours, at the end of the enema, and fell to 1.4 mg. one hour later. Subject D started with a level of 1.6 mg. per hundred cubic centimeters, rose to 3.4 mg. at two and one-half hours, the end of the enema, and fell to 3.0 mg. one hour later. Although in none of these 3 subjects did high levels of magnesium in the serum develop, and none exhibited central effects, it is to be noted that all showed some elevation of the magnesium level, with increases varying from 1.3 to 1.8 mg. per hundred cubic centimeters.

Subject C was successful in keeping the tube in the rectum throughout the three hours of his enema, and it may be assumed that he received the full 94 Gm. His initial serum magnesium level was 1.4 mg. per hundred cubic centimeters. After one and one-half hours the level was 3.3 mg. per hundred cubic centimeters, and the subject reported that he was beginning to feel warm all over. At two hours, he noted dryness of the lips and tongue. At two and one-half hours, the serum magnesium level was 7.0 mg. per hundred cubic centimeters, and the sensations of warm skin and dry mouth were intensified. Thirty minutes later, the enema was completed, and the subject remarked that the warm feeling was diminishing. One hour later, the magnesium level was 5.0 mg. per hundred cubic centimeters, and he claimed not to feel any different than usual. At no time did this subject display signs of drowsiness (chart 1).

Subject E received 250 cc. of a saturated solution of magnesium sulfate over a period of three hours, and since the rectal tube was retained it may be assumed that he received the full amount of 158 Gm. At the start, the serum magnesium was 1.5 mg. per hundred cubic centimeters, and the subject was conversing volubly, in his usual manner. At one hour and ten minutes, the serum level was 2.2 mg. per hundred cubic centimeters, and there were no symptoms. At one and one-half hours, the subject noted that his mouth was getting dry and his skin warm. At two hours and fifteen minutes, the serum magnesium was 7.0 mg. per hundred cubic centimeters, he said he was getting drowsy and there was a marked diminution in his speech activity. At three hours, the drip was stopped, after 158 Gm. of the salt had been admin-

istered, because the subject had become much more drowsy. The serum magnesium level was 12.1 mg. per hundred cubic centimeters. He lay quietly, breathing heavily and deeply, with eyes closed, and it required two or three commands or a rough shake to rouse him, on which he would speak thickly and slowly a few words and then fall asleep again. At this point, 1 Gm. of calcium gluconate was injected intravenously, and improvement was noted within one minute, it being easier to rouse him. Five minutes after the injection, he spontaneously remarked, "Now, I'm coming out of it." However, fifteen minutes later, he had

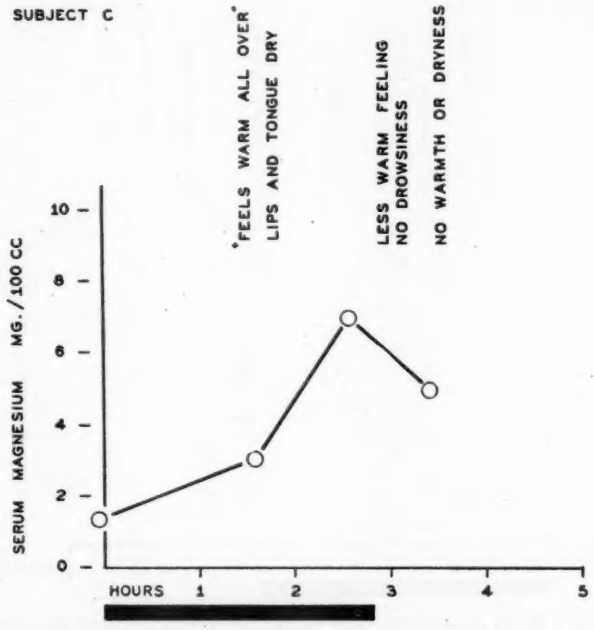

Chart 1.—Serum magnesium levels for subject C, who received per rectum 300 cc. of one-half saturated solution of magnesium sulfate, containing 94 Gm. of the salt.

lapsed into his previously depressed state, and another 1 Gm. of calcium gluconate was therefore administered. There was another slight improvement within five minutes; but it, too, was short lived, and he returned to a deep sleep, with snoring and deep respirations, from which he could be roused only with difficulty. Examination disclosed diaphragmatic respiration, active tendon reflexes and no pathologic reflexes. At this point the heart rhythm was grossly irregular, with a rate of about 100 a minute. The electrocardiogram showed auricular fibrillation. The subject slowly became less drowsy, and one hour after the

administration of the enema the serum magnesium level was 16.2 mg. per hundred cubic centimeters. A tap water enema was given, in order to evacuate any magnesium sulfate remaining in the rectum. Water was forced by mouth, and a high output of urine was maintained. The subject regained consciousness rapidly, passing in twenty minutes from a state of sleep, from which he could be roused to converse in thick speech, to a state of mild excitement, during which he sat up, talked in a loud manner, demanded to read the newspaper and called for food. He ate lunch, listened to the radio and remained in a state of relative excite-

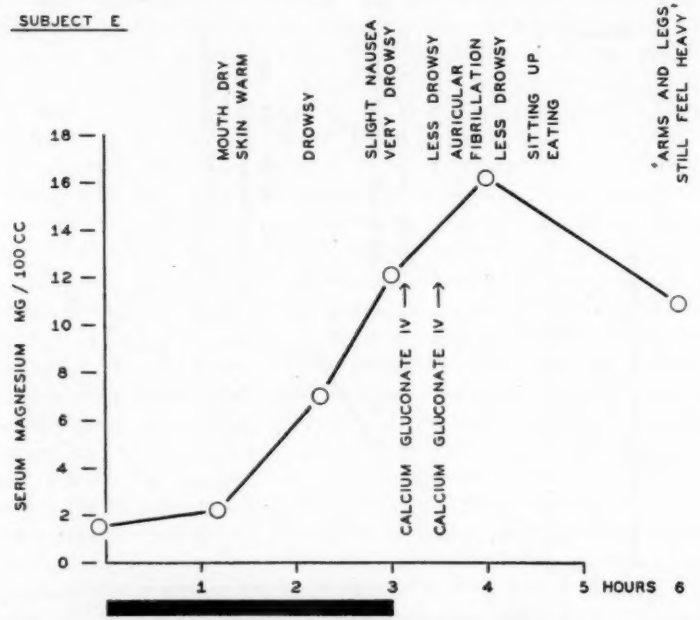

Chart 2.—Serum magnesium levels for subject E, who received per rectum 250 cc. of a saturated solution of magnesium sulfate, containing 158 Gm. of the salt.

ment for several hours. Three hours after the enema, the serum magnesium level had fallen to 10.9 mg. per hundred cubic centimeters, at which point the subject declared that his extremities felt heavy, but he was otherwise well (chart 2). However, auricular fibrillation was still present, and it persisted about four hours after it was first noted, when the rhythm reverted to normal.

Subject F received 200 cc. of saturated solution of magnesium sulfate over a period of two and one-half hours. It may be assumed that he received the whole 126 Gm. At the start, the serum magnesium level was 0.4 mg. per hundred cubic centimeters. Dry mouth and warm

skin were reported a full half-hour before blood was drawn, which showed a serum magnesium level of 2.3 mg. per hundred cubic centimeters, and it is doubtful whether the early symptoms represented a true effect of magnesium in this patient, who was a medical student and anxious to perform well. However, after two hours and fifteen minutes, the serum level was 5.3 mg. per hundred cubic centimeters, and the mouth was reported drier and the skin very warm. He was slightly drowsy, stared listlessly at the window, allowed the newspaper to fall on the bed and occasionally closed his eyes. After two and one-half

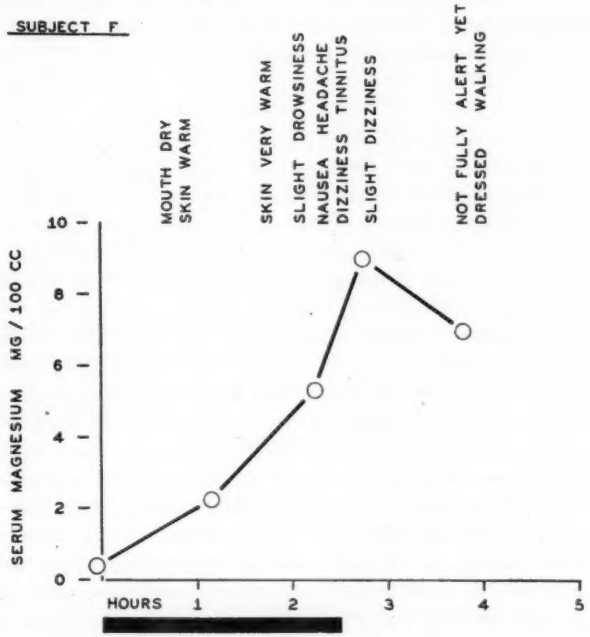

Chart 3.—Serum magnesium levels for subject F, who received per rectum 200 cc. of a saturated solution of magnesium sulfate, containing 126 Gm. of the salt.

hours, the drip was stopped, after 126 Gm. had been given, because of nausea, dizziness, a feeling of approaching syncope, headache and tinnitus. It is inferred that these symptoms were nonspecific, for they disappeared entirely in a few minutes. Ten minutes after the enema had been terminated, the serum magnesium was 9.0 mg. per hundred cubic centimeters, and the subject felt only slightly drowsy, with the same warm skin and dry mouth. All the symptoms gradually diminished, and one hour and twenty minutes after the end of the drip administration, the serum level was 7.0 mg. per hundred cubic centimeters,

and the subject felt well except for a feeling of apathy. He did not exhibit evidence of excitement (chart 3). It is of interest to note that neither of the 2 subjects who received the saturated solution of magnesium sulfate complained of local irritation.

Series 2.—Each of 3 subjects was given 40 cc. of saturated solution of magnesium sulfate by mouth, and specimens of blood were drawn at intervals thereafter. All of them showed some increase in the serum magnesium, the peak values being 4.0, 3.6 and 4.3 mg. respectively, per hundred cubic centimeters. It is suggested that some of the feeling of well-being so often experienced by persons who take a magnesium sulfate purge is secondary to a central sedative effect, rather than being due entirely to the relief of constipation.

COMMENT

From the evidence in the literature, and from the results reported in the preceding section, it is obvious that magnesium sulfate is absorbed from the gastrointestinal tract, including the rectum, in amounts sufficient to raise significantly the blood level and to produce depressant cerebral effects. Even normally functioning kidneys may not remove the salt from the blood stream fast enough to prevent the accumulation of amounts toxic to the central nervous system.

In our experience with 6 human subjects, the normal serum magnesium was in the range of 1.5 to 2.5 mg. per hundred cubic centimeters. Sensations of warm skin and dry mouth began at a level of about 4 mg. per hundred cubic centimeters. Drowsiness was noted at about 7 mg. per hundred cubic centimeters and became marked in the neighborhood of 12 mg. per hundred cubic centimeters. Between the levels of 12 and 16 mg., 1 subject was noted to exhibit diaphragmatic respirations, although they were maintained at average depth and rate. Respiratory arrest occurred only in the fatal case, in which the postmortem serum magnesium level was 20.1 mg. per hundred cubic centimeters. In 1 subject, a man aged 42 without evident heart disease, auricular fibrillation was present for about four hours during the highest levels of magnesium in the blood. It was not noted until after calcium had been administered, and the origin and significance of the abnormal rhythm are confused.

The total amount of magnesium sulfate U. S. P. administered may be roughly correlated with the height of the serum magnesium level reached. In 3 subjects given 25 Gm. of magnesium sulfate by mouth, the serum magnesium reached levels of approximately 4 mg. per hundred cubic centimeters, the highest being 4.3 mg. per hundred cubic centimeters. In the subject known to have received 94 Gm. of the drug per rectum, the serum magnesium reached a level of 7.0 mg. per hundred cubic centimeters; in the subject receiving 126 Gm. per rectum it

reached a level of 9.0 mg., and in the subject receiving 158 Gm. it reached a level of 16.2 mg. The patient receiving 189 Gm. had a postmortem level of 20.1 mg. per hundred cubic centimeters. The time factor was approximately constant, since all the enemas took about three hours. It is likely that the serum level reached with any given amount of magnesium sulfate will vary inversely with the duration of administration of the drug, the renal excretion and rectal leakage remaining constant.

It is inferred that an agent has been used in large amounts for oral and rectal administration with a sense of security that may not be justified. Magnesium sulfate may be absorbed rapidly, and dangerous concentrations in the blood may be reached even in the presence of normal renal function. For rectal administration, amounts of more than 94 Gm. over a three hour period are contraindicated. In amounts of this magnitude, or in smaller amounts given over a short period, as in a "magnesium, glycerin, water" enema, the patient should be carefully observed for signs of toxicity due to magnesium, namely, flushed skin with a feeling of warmth, dry mouth and, especially, increasing drowsiness. If the last sign appears, the procedure should be discontinued, the rectum washed out with tap water and fluids forced by mouth or vein. Calcium should be administered intravenously, although its effect as an antidote may be disappointingly temporary and repeated administration be necessary. The administration of magnesium sulfate by any route in a patient with impaired renal function is a hazardous procedure.

SUMMARY

A review of the literature on magnesium intoxication, together with a discussion of the pharmacology of magnesium sulfate, is presented.

The protocol of a patient exhibiting fatal magnesium intoxication is presented. The clinical phenomena of a second patient who, after receiving magnesium sulfate, became dangerously depressed are also described.

Hypertonic solution of magnesium sulfate was given per rectum to 6 male subjects, and significant absorption into the blood stream was demonstrated by measuring the serum levels. The latter were correlated with symptoms and signs of magnesium intoxication, notably a feeling of warm skin, dry mouth and drowsiness.

It has further been demonstrated that magnesium sulfate can be absorbed in large amounts from the intact bowel and may cause dangerous depression of the central nervous system, even in the presence of normal renal function. Limitations of the amount of magnesium sulfate to be administered are suggested, and a procedure is proposed for the management of a patient with signs of intoxication.

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PSYCHOMETRIC PATTERNS ASSOCIATED WITH MULTIPLE SCLEROSIS

I. Wechsler-Bellevue Patterns

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SINCE Charcot and Vulpian, in 1860, first recognized the condition of multiple sclerosis as a disease *sui generis,* studies on the etiology, prognosis and treatment of this clinical entity have been carried out predominantly in the field of medicine.

In recent years, however, scientific interest has shifted to include the psychologic implications of multiple sclerosis, since a purely physiologic and mechanistic approach has thus far been relatively unproductive. There has been evidence that this shift in emphasis has opened more promising avenues of research, which warrant thorough investigation.[1]

Accordingly, the group of patients with multiple sclerosis at the Veterans Administration Hospital at Fort Thomas have been made the subjects of an investigation in which psychologic evaluation comprises an integral part. The initial stage of this investigation is concerned with complete psychologic measurements. This, the first, report deals with the results of the Wechsler-Bellevue tests; a subsequent report will deal with the evaluation of results of the Rorschach test.

The purpose of this study is the investigation of each aspect of intellectual functioning in a group of patients with multiple sclerosis, the procedures including (1) range and distribution of Wechsler-Bellevue intelligence quotients; (2) determination of sub test "pattern-

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This study was conducted under the supervision of Thelma E. Brown, Ph.D., Chief Clinical psychologist, Veterans Administration Hospital.

Sponsored by the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are a result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

1. Scheinker, I. M.: Recent Advances in Research and Treatment of Multiple Sclerosis, Ohio State M. J. **45**:27 (Jan.) 1949. Aring, C.: Recent Advances from a Study of Multiple Sclerosis, ibid. **45**:31 (Jan.) 1949. Langworthy, O. R.: Relation of Personality Problems to Onset and Progress of Multiple Sclerosis, Arch. Neurol. & Psychiat. **59**:13 (Jan.) 1948.

ing" and a comparison with the "normal" ; (3) evaluation of signs of organic damage to the brain in the group, as revealed by Wechsler's clinical signs, and (4) the relationship of signs of organic disease to Wechsler's index of deterioration.

HISTORICAL REVIEW

Wechsler [2] first made reference to the use of deviations of subtest scores from a mean level in the diagnostic application of his scale. He stated:

> . . . We have accumulated sufficient clinical experience with the Bellevue Scale to warrant a presentation of certain empirical findings which we believe will be of use to the clinician in his attempts at diagnosis.

Few references may be found in the literature in which this procedure has been utilized in the differential diagnosis of multiple sclerosis. Burgemaster and Tallman [3] reported:

> Wechsler-Bellevue scores range from 80-135 with the group mean at 101. . . . A wide discrepancy between remote and recent memory . . . suggests a lowering of the present level of functioning and the difficulty in assimilating new material quickly. Numerous features point to an organic basis for this impairment.

Langworthy, Kolb and Androp,[4] in their investigation of the behavior of patients with multiple sclerosis, stated:

> The disease, as far as the mental symptoms are concerned presents an inconsistency, irregularity and polymorphism which exactly corresponds to the irregular and polymorphic nature of the [multiple sclerosis] lesions.

Borberg and Zahle [5] reported:

> The pathologico-anatomical localisation determining the mental symptoms [in multiple sclerosis] has not yet been settled. . . . Most likely, however, the occurrence of the disease is based less on the well-defined focal lesions than on more extensive changes.

There is, however, a concurrence of opinion in the medical literature on the concept of a basic neuropathologic process involving nonspecific and multiple areas within the brain and spinal cord of the patients with multiple sclerosis. It has been stated [3] that such a patient displays signs of organic damage to the brain. Since this concept was not consistent with subjective observations on the group of patients in the present study, investigation of this particular point was also planned.

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2. Wechsler, D.: The Measurement of Adult Intelligence, Baltimore, Williams & Wilkins Company, 1944.

3. Burgemaster, B. B., and Tallman, G.: Rorschach Patterns in Multiple Sclerosis, Rorschach Research Exchange **60**:111, 1945.

4. Langworthy, O. R.; Kolb, L. C., and Androp, S.: Disturbances of Behavior in Patients with Disseminated Sclerosis, Am. J. Psychiat. **98**:243 (Sept.) 1941.

5. Borberg, N. C., and Zahle, V.: On the Psychopathology of Disseminated Sclerosis, Acta Psychiat. **21**:74, 1946.

PRESENT STUDY AND COMMENT

Twenty-four patients with multiple sclerosis were used in this study. Some records were discarded because physical incapacitation prevented administration of the performance section of the test and full scale intelligence quotients, etc., could not be calculated.

TABLE 1.—*Distribution of Full Scale Intelligence Quotients*

Classification	Range of Intelligence Quotients	Number of Patients
Very superior	128 +	1
Superior	120-127	1
Bright normal	111-119	5
Average	91-110	10
Dull normal	80-90	2
Borderline	66-79	2
		22

TABLE 2.—*Summary of Statistical Findings*

	Verbal Section				
Statistic	Information	Comprehension	Digit Span	Arithmetical Calculations	Similarities
N	24	24	24	24	24
Mean	11.04	10.96	7.05	10.04	10.92
σ	2.57	2.75	3.03	3.73	2.86
Standard error of mean	0.54	0.57	0.63	0.78	0.59
Standard error of difference between M_1 and M_2	0.56	0.59	0.65	0.80	0.61
t	1.864	1.626	3.130*	0.050	1.500
$t0.05 = 1.968$					
$t0.01 = 2.592$					

	Performance Section				
Statistic	PA	Picture Completion	Block Design	Object Assembly	Digit Symbol
N	21	21	21	21	20
Mean	9.14	11.43	8.62	8.43	6.90
σ	2.51	2.17	2.84	3.34	2.08
Standard error of mean	0.56	0.49	0.64	0.75	0.48
Standard error of difference between M_1 and M_2	0.58	0.51	0.65	0.76	0.59
t	1.472	2.900*	2.108†	2.057†	6.163*
$t0.05 = 1.968$					
$t0.01 = 2.592$					

* Less than 1:100 probability of being due to chance alone.
† Less than 5:100 probability of being due to chance alone.

Table 1 shows the distribution of intelligence quotients obtained.

It was of additional interest to determine the amount and direction of any deviation in this group from Wechsler's standardization group (mean, 10; standard deviation, 3). Table 2 presents these findings.

It is shown in table 2 that group subtest means deviated from the "normal," or expected mean, by a significant amount in five subtests:

(1) digit span, (2) picture completion, (3) digit symbol, (4) object assembly and (5) block design.

However, success on the latter three tests depends greatly on motor skill and the earning of "time bonuses" given for rapid and deft performance of arm-hand movements. The patient with multiple sclerosis, because of his physical handicaps, does less well in these tasks for the same reasons that the amputee or the paralyzed patient, who has motor impairment but no organic damage to the brain, does poorly. Parsimonious interpretation of these results dictates the conclusion that poor performance on the last three tests is not a "diagnostic sign" of multiple sclerosis per se. Patients with multiple sclerosis usually exhibit motor impairment and, *ipso facto,* will perform poorly on such motor tests.

The deviations noted on digit span and picture completion subtests, however, admit of different interpretation. The recall of digits has a large intellectual component and only minimal motor components. The significantly low scores on the digit span test may be indicative of the presence of anxiety or tension, which interferes with the exercise of full ability, or it may be the characteristic behavior of the patient with organic damage to the brain. Additional evidence will be necessary to define the cause of the depression in the test score.

The picture completion test involves nearly the same general skills as the digit span test, with the additional requirement of accurate visual perception. According to Wechsler [2]:

> This test measures the individual's basic perceptual and conceptual abilities insofar as these are involved in the visual recognition and identification of familiar forms and objects. . . . the ability of the individual to differentiate essential from unessential details.

Success in this test, therefore, may represent compensatory action by the patient with multiple sclerosis who recognizes his motor limitations, as well as the "nonmotor" skills required by the test.

The next point of consideration was the number of "organic signs" appearing in each record. Signs of organic damage to the brain are the particular subtest successes and failures given by Wechsler as characteristic of the performance of patients with such organic damage.

The average number of signs per patient was 4.8 out of a possible 12, with a range of 3 to 7 signs. Table 3 shows the contribution of each subtest to the total number of signs.

Examination reveals that the subtests contributing most heavily (frequency of 50 to 90 per cent) to the picture of organic damage to the brain are those which require motor skill in greater or less degrees. The interpretation here is the same as that for the aforementioned three subtests (digit symbol, object assembly and block design); i. e., the appearance of signs of organic damage may be the result of physical handicap alone, and may not necessarily be indicative of cortical lesions.

Even with the impairment in psychomotor performance, the number of signs of organic damage exhibited by these patients are not sufficient to be diagnostically significant.

TABLE 3.—*Frequency of Appearance of "Organic" Signs in Wechsler-Bellevue Subtests*

Subtest	Frequency	Percentage of N *
Object assembly	18	90
Block design	17	85
Verbal > performance †	12	60
Digit symbol	10	50
Picture arrangement	10	50
Digit span	10	50
Comprehension	7	35
Information	6	30
Arithmetic	1	5
Similarities	1	5
Vocabulary	1	5

* N (Number of subjects) = 20.
† Sum of verbal subtests vs. sum of performance subtests.

TABLE 4.—*Relation of Deterioration to Signs of Organic Cerebral Damage*

Subject	Deterioration, %	Number of Signs
1	0	6
2	0	6
3	7	5
4	9	4
5	17	5
6	0	3
7	15	4
8	32	4
9	4	5
10	1	5
11	46	5
12	60	6
13	34	4
14	0	4
15	9	3
16	6	5
17	24	7
18	2	5
19	23	5
20	0	4

The data allow an interesting comparison between the presence of signs of organic damage to the brain and the index of deterioration, also furnished by the Wechsler-Bellevue scale. With use of Wechsler's signs of organic damage to the brain, applying them in the formula for the index of deterioration, on the basis of the values given [4] (page 153) and employing his standarization mean of 10, we found that the amount of deterioration theoretically associated with a patient who

exhibited all of the signs of organic damage to be in the order of 0.28. This suggests that the correlation of signs of organic damage to the brain and the index of deterioration should be present and positive. The results for the individual patients are given in table 4. Wechsler did not consider the index of deterioration to be significant until it reaches from 0.20 to 0.30 or higher.

A Pearson product moment correlation was calculated for these data and found to be 0.17 ± 0.223. No significant relation was demonstrated between the variables. This is further evidence of the absence of measurable intellectual impairment concomitant with the signs of organic damage to the brain in this group.

SUMMARY

A series of 24 patients with a condition diagnosed as multiple sclerosis were subjected to psychometric evaluation. The results are reported. Interpretation must be cautious, owing to the small number of subjects (N).

The distribution of intelligence quotients in the group was essentially normal.

Statistical analysis revealed that these patients showed significant departures from "normal" performance in two respects: (1) a low memory span for digits forward and backward, and (2) better than average visual concentration and attention in the picture completion subtest.

Despite expectations, the correlation of test measures of intellectual deterioration and quantitative "signs" of organic cortical damage was not significant. The average number of signs of organic impairment noted in the individual records would be of inconclusive value in differential diagnosis on the basis of the Wechsler-Bellevue test alone. The foregoing data lead to one of two tentative conclusions:

1. Quantitative signs of organic damage to the brain, or the index of deterioration on the Wechsler-Bellevue scale, is inadequate as an indicator of existing cortical damage in multiple sclerosis.

2. No cortical pathologic changes existed in the population with multiple sclerosis comprising this study.

Further study of these patients by means of projective test instruments should add valuable information concerning the intellectual and psychic makeup of the patients with multiple sclerosis.

INTERACTION OF EFFECTS OF ACETYLCHOLINE AND ADENOSINE TRIPHOSPHATE ON ELECTRICAL ACTIVITY OF CAT CEREBRAL CORTEX

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IN THE course of an investigation into effects on the electrical activity of the cat cerebral cortex exerted by substances known to be present in nerve tissue, we have studied the interaction between acetylcholine and adenosine triphosphate after their successive local application to the cortex. We consider the findings suggestive enough to justify a separate description. Our attention was directed to the investigation of this interaction by the demonstration of Nachmansohn [1] that adenosine triphosphate plays a role in the synthesis of acetylcholine by nerve tissue, under certain conditions, in vitro.

METHOD

The results of experiments on 22 mongrel adult cats are reported here. Anesthesia was induced by the intraperitoneal injection of pentobarbital sodium, U. S. P., in a dose of 0.060 Gm. (1 grain) per kilogram of body weight. If, during a long experiment, the need arose for further anesthesia, an intraperitoneal injection of about 0.016 Gm. of pentobarbital sodium was given. The cerebral cortex was exposed widely, usually on the left side, occasionally bilaterally. Absorbent cotton wool wick electrodes were employed, each soaked in 0.9 per cent sodium chloride solution and wrapped around silver wire soldered to a shielded copper wire, which, in turn, was led to a model III four channel Grass electroencephalograph, for amplification and recording of the potential changes.

One electrode was placed on the cortex in the region of the motor cortex, and another, just anterior to the occipital lobe, as defined by gross anatomic observation. Because of the objective of these experiments, it was not considered necessary to confirm the placement of electrodes by accurate anatomic or physiologic procedures. An indifferent electrode was formed either through metal buttons attached by collodion to each of the animal's ears or by a similar button placed on

1. Nachmansohn, D., and Machado, A. L.: The Formation of Acetylcholine: A New Enzyme; "Choline Acetylase," J. Neurophysiol. **6**:397, 1943.

the skin of the left maxillary region. Activity was then recorded between the two cortical electrodes and between each cortical electrode and the indifferent one.

The acetylcholine was dissolved in 0.9 per cent sodium chloride in water in a concentration of 10 per cent. In some experiments, neostigmine methylsulfate was added to the 10 per cent acetylcholine solution in a final concentration of 0.25 per cent. In experiments in which the neostigmine was applied separately, it was prepared in the form of a 0.25 per cent solution in 0.9 per cent sodium chloride in water. The adenosine triphosphate (in the form of the water-soluble sodium salt) was dissolved in 0.9 per cent sodium chloride in water in a concentration of 2.5 per cent. These concentrations are expressed in terms of weight of solute in volume of solvent.

Acetylcholine and adenosine triphosphate solutions were made up daily from the stock supplies kept in the solid state at — 18 C. The vials of neostigmine were kept at 0 C. None of the compounds used in the experiments reported here was studied for purity in our laboratory. However, each new lot of adenosine triphosphate was checked for its effect in producing a reversible decrease in the flow birefringence of actomyosin solution.[2]

The p_H of solutions placed on the cortex was approximately 6.9, as measured with a glass electrode. Observations reported by Hyde, Beckett and Gellhorn[3] make it probable that precise control of the p_H in the range from 3 to 11 units is unimportant when solutions are applied to the cortex by means of rather small pledgets. These investigators have found also that when this method of local application is employed, varying the osmotic pressure of sodium chloride solutions from an iso-osmotic concentration to approximately twenty-fold that concentration does not influence either normal or convulsive patterns of electrical activity. Similarly, we did not obtain significant changes in electrical activity of the cortex after local application of sodium chloride controls varying from iso-osmotic to four times iso-osmotic pressure; this range more than covered the calculated increase in osmotic pressures effected by our test substances.

The compounds were applied to the cortex by means of flat absorbent cotton pledgets which were soaked in the solution to be studied. These pledgets were squares, approximately 6 mm. on a side. In the early experiments, the pledgets were left on the cortex for one to two minutes and then removed, and an electrode was placed over the area of the cortex which had been treated. In most of the experiments, pledgets were placed on the cortex either anteriorly or posteriorly, and the recording electrode was placed over them. After removal of a pledget from the cortex, the area was washed with warm saline solution and the cotton wick electrode renewed. Removal of a pledget, washing of the cortex, placing of a new pledget and adjustment of the electrode could be accomplished within forty-five to sixty seconds.

RESULTS

Many investigators have observed that the local application of acetylcholine, acetylcholine and physostigmine, or acetylcholine and neostigmine has an excitatory effect on the cerebral cortex, as evidenced by the

2. Jordan, W. K., and Oster, G.: On the Nature of the Interaction Between Actomyosin and ATP, Science **108**:188-190 (Aug. 20) 1948.

3. Hyde, J.; Beckett, S., and Gellhorn, E.: Acetylcholine and Convulsive Activity, J. Neurophysiol. **12**:17-27, 1949.

appearance of many spikes in the record of cortical electrical activity.[4] Brenner and Merritt[4d] pointed out the resemblance of the electrical effects evoked by acetylcholine to the pattern of activity observed in grand mal seizures. As our illustrations show (figs. 1, 2 and 3), we have observed effects similar to those previously described. In none of the reports seen by us have we found very exact information concerning the frequency of occurrence of the response. The effect is usually described as occurring in a "majority of instances," or "often" or "occasionally," with various more or less favorable concentrations of acetylcholine and neostigmine or sites of application. In view of the many parameters concerned in the appearance of such an effect, this is, of course, wise. However, since our findings with regard to the acteylcholine response may serve as an index to evaluation of unmeasured parameters, such as the level and type of anesthesia[4e] in relation to the other

Data on Interaction of Effects of Acetylcholine and Adenosine Triphosphate on Cat Cerebral Cortex

	Acetylcholine			Adenosine Triphosphate					
							Frequency of Grades of Effect		
Number of Experiments	Applications	Excitatory Response	Percentage	Applications	Effects	Percentage	Grade	Frequency	Duration
22	53	31	58	43	35	80	1 2 3 4	8 6 12 9	Average, 14 min.; extremes, 1 min. and 1.2 hr.

effects described in this paper, we offer our results in tabular form. We observed the excitatory response in 58 per cent of 53 applications (table).

Topical application of adenosine triphosphate to an area treated approximately five minutes previously with acetylcholine and neostigmine may result in an alteration in local electrical activity of the cortex (fig. 1). We encountered the adenosine triphosphate response in 80 per cent of 43 applications (table).

4. (*a*) Sjöstrand, T.: Potential Changes in the Cerebral Cortex of the Rabbit Arising from Cellular Activity and the Transmission of Impulses in the White Matter, J. Physiol. **90**:41P-45P, 1937. (*b*) Miller, F. R.; Stavraky, G. W., and Woonton, G. A.: Effects of Eserine, Acetylcholine and Atropine on the Electrocorticogram, J. Neurophysiol. **3**:131-138, 1940. (*c*) Chatfield, P. O., and Dempsey, E. W.: Some Effects of Prostigmine and Acetylcholine on Cortical Potentials, Am. J. Physiol. **135**:633-640, 1942. (*d*) Brenner, C., and Merritt, H. H.: Effect of Certain Choline Derivatives on Electrical Activity of the Cortex, Arch. Neurol. & Psychiat. **48**:382-395 (Sept.) 1942. (*e*) Forster, F. M.: Action of Acetylcholine on Motor Cortex: Correlation of Effects of Acetylcholine and Epilepsy, ibid. **54**:391-394 (Nov.-Dec.) 1945.

We have arbitrarily divided these adenosine triphosphate effects into four grades (table; fig. 1). The grade 1 effect is defined in terms of a decrease in number or abolition of spikes induced in the record by acetylcholine and neostigmine. Those responses are placed under grade

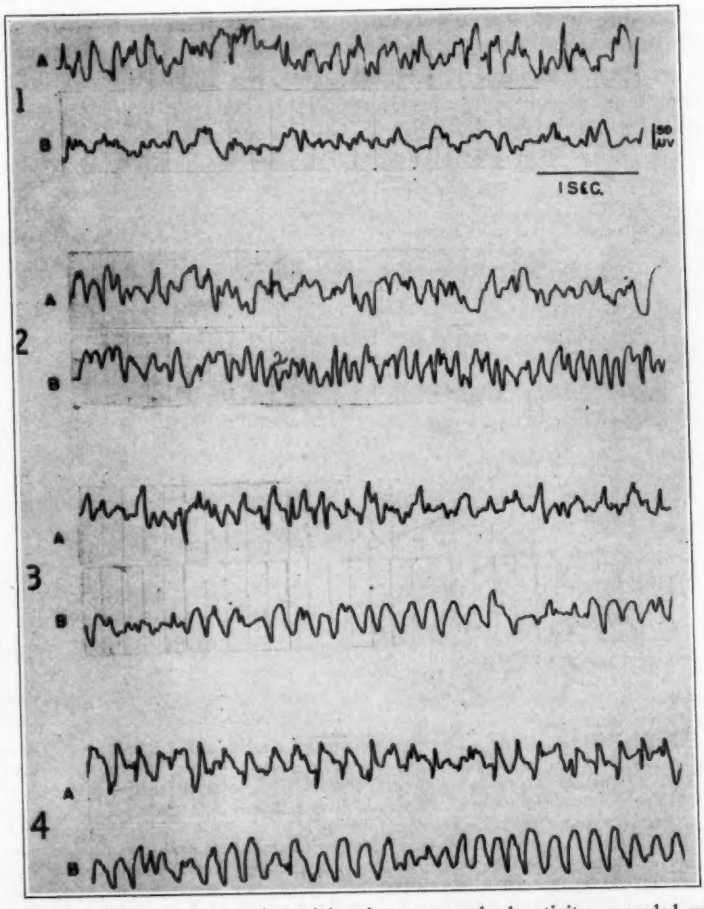

Fig. 1.—Effects of adenosine triphosphate on cerebral activity, recorded with bipolar leads. Acetylcholine and adenosine triphosphate were placed successively under the posterior electrode. *A*, a record of cortical activity from one to ten minutes after application of acetylcholine and one minute before application of adenosine triphosphate. *B*, a record of cortical activity approximately one minute after application of adenosine triphosphate. The grade of activity is indicated by arabic numerals to the left of the records.

2 which resemble the waking type of electrical pattern seen in the cat. Those effects are classified as grade 3 in which there are both a dis-

appearance of the spikes present in the preceding record and the appearance of rather regular, ordered, slow, smooth waves of 4 to 6 per second frequency. Under grade 4 are placed those responses which are similar to the grade 3 effect but are marked by greater degree of regularity of the 4 to 6 per second frequency.

Moving an exploratory electrode about outside and within the area of treated cortex revealed that the alteration in electrical activity was rather sharply localized to a region under or within 8 or 9 mm. of the edge of the pledget by means of which the adenosine triphosphate was applied to the cortex. On four occasions (during a grade 4 response) the adenosine triphosphate effect spread over the hemisphere to which

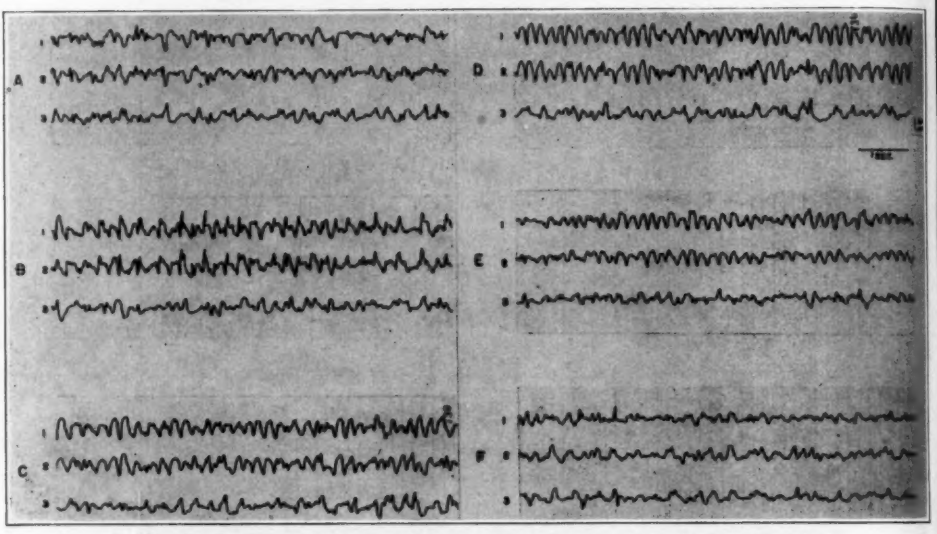

Fig. 2.—Reversal of the acetylcholine effect by adenosine triphosphate. Channel *1:* bipolar leads: electrodes placed anteriorly and posteriorly on the cortex. Channel *2:* monopolar leads: activity between the posterior and the indifferent electrodes. Acetylcholine and adenosine triphosphate were placed successively under the posterior electrode (electrode common to channels *1* and *2*). Channel *3:* monopolar leads: activity recorded between anterior and indifferent electrodes. *A*, control record; *B*, acetylcholine response, in channels *1* and *2*, about one minute before application of adenosine triphosphate; *C*, twenty seconds after application of adenosine triphosphate, showing effect of the drug, grade 4, in channels *1* and *2; D*, three minutes, and *E*, ten minutes, after application of adenosine triphosphate, both showing effect of application of adenosine triphosphate in channels *1* and *2; F*, forty minutes after application of adenosine triphosphate, and eighteen minutes after its removal, showing return of the record to the control type of activity.

the drug was applied. (In none of these instances had the acetylcholine response elicited previously spread from the site of application.) In 5 experiments in which bilateral cortical electrodes were in place and

during which good unilateral adenosine triphosphate effects were obtained, we did not observe spread to the opposite hemisphere, although in the course of analyzing the effects of applying adenosine triphosphate to different projective areas of the cortex one may encounter this phenomenon.

On at least 6 occasions washing of the cortex with warm saline solution after an adenosine triphosphate effect had diminished or dis-

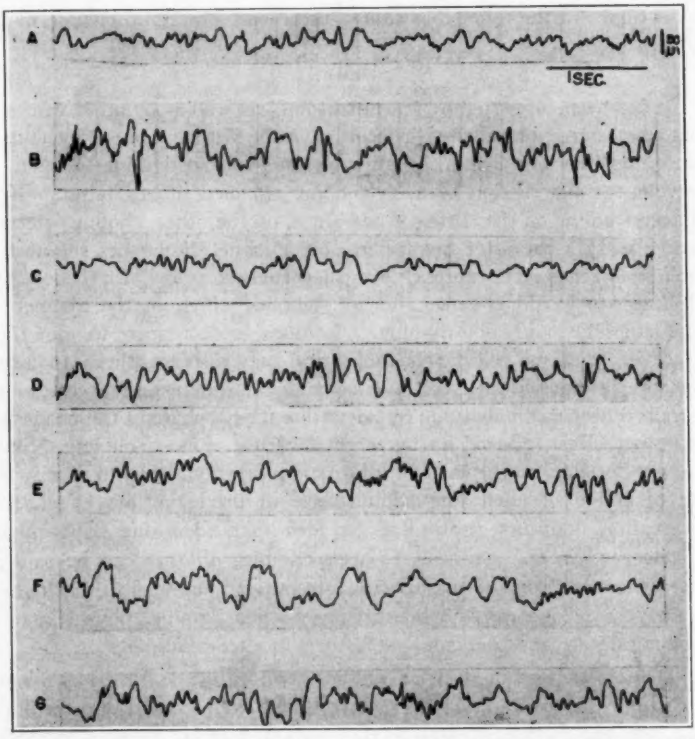

Fig. 3.—Reversal of acetylcholine effect by application of adenosine triphosphate, recorded with bipolar electrodes. Acetylcholine and adenosine triphosphate were placed successively under the posterior electrode. *A*, control record; *B*, acetylcholine response, about one minute before application of adenosine triphosphate; *C*, twenty seconds after application of adenosine triphosphate, showing grade 1 response to the drug, with abolition of spikes induced by acetylcholine; *D*, five minutes; *E*, ten minutes, and *F*, twenty minutes, after application of adenosine triphosphate; *G*, forty minutes after application of adenosine triphosphate, and twenty-two minutes after its removal from the cortex.

appeared resulted in considerable augmentation of the response to the drug. In 2 instances after the cortex had been washed in such circumstances, reappearance of an acetylcholine type of response was noticed.

On 15 occasions of 17 in which adenosine triphosphate was applied to the local area during the course of a convulsive type of acetylcholine effect, there was a pronounced alteration in the local electrical activity; this alteration took the form of some one of the grades of the adenosine triphosphate effect previously described (figs. 2 and 3). In 1 of the experiments in which adenosine triphosphate failed to induce its effect, there were an increase in regularity of the acetylcholine-induced spiking and some increase in amplitude of the spikes, as judged by visual inspection. In the other experiment there was simply no change in the pattern.

COMMENT

It has been suggested by Nachmansohn,[1] as well as by other workers, that adenosine triphosphate is concerned in the synthesis of acetylcholine.[5] Since, on the one hand, neostigmine and physostigmine, known to prevent the destruction of acetylcholine, enhance the excitatory effect of acetylcholine on the cortex [4b] and since, on the other, choline esterase, known to split the ester linkage in acetylcholine, diminishes the acetylcholine effect on the cortex,[6] we suspected, a priori, that adenosine triphosphate would enhance the acetylcholine effect in the manner of physostigmine and neostigmine. It does not appear to do that. However, it seems reasonable to us, and may also to others, to interpret the interaction between adenosine triphosphate and acetylcholine described here as an abolition by adenosine triphosphate of the particular excitatory effect induced in the cerebral cortex by acetylcholine. Since it is not possible, on the basis of information now available, to specify the site of action of adenosine triphosphate in producing its effect, this observation does not contradict the idea that adenosine triphosphate is concerned in the synthesis of acetylcholine; all that can be said at the moment is that it seems difficult to relate our findings to that notion as directly as one can the interactions of neostigmine, physostigmine, choline esterase and acetylcholine to their in vitro relations.

That the pattern of electrical activity induced in the cortex by adenosine triphosphate is quite different from the well known one resulting from the application of strychnine [7] may reflect, in turn, a different pattern of firing of the neurons affected by these compounds. Thus, the adenosine triphosphate effect may be of some use as a physiologic

5. Olsen, N. S., and Klein, J. R.: Effect of Convulsive Activity of Brain upon Its Carbohydrate Metabolism: Epilepsy, A. Research Nerv. & Ment. Dis., Proc. **26**:118-30, 1947.

6. Beckett, S., and Gellhorn, E.: Role of Acetylcholine in the Activity of Sensori-Motor and Suppressor Areas of the Cortex, Am. J. Physiol. **153**:113-120 (April) 1948.

7. Dusser de Barenne, J. G.: Experimental Researches on Sensory Localizations in the Cerebral Cortex, Quart. J. Exper. Physiol. **9**:355-390, 1916.

tool for ordering the activity of an area of cortex in a manner different from that of the usual activation by strychnine.

It is interesting, also, to note that pyruvic acid, which is known to inhibit the production of acetylcholine in vitro,[8] has a slight anticonvulsant action when tested by the electrical threshold method of Putnam and Merritt.[9] Indeed, these investigators have termed pyruvic acid a physiologic anticonvulsant. This observation, coupled with our interpretation of the adenosine triphosphate effect, both involving naturally occurring compounds known to influence acetylcholine metabolism, as well as being of fundamental importance in the glucose metabolism, may serve to support the hypothesis of Brenner and Merritt [4d] that a disturbance in acetylcholine metabolism is etiologically important in certain varieties of epilepsy. A disturbance in the usual balance of the metabolic interrelations of these physiologically occurring substances with opposing effects on the organization of activity of the cortex may lead to the appearance of the excitatory effect of acetylcholine.[9] This possibility suggests a search for other interactions similar to the one described here among the constituents of neurons known to be of metabolic importance and related to acetylcholine metabolism.

Finally, it follows from our interpretation of the adenosine triphosphate effect, as an abolition of the convulsant acetylcholine response, that it would be of concern to know whether adenosine triphosphate is effective in raising the threshold to electrically induced convulsions and whether it has any influence on the various forms of epilepsy occurring in man.

SUMMARY

The topical application of a 2.5 per cent solution of adenosine triphosphate to a region of cortex previously treated with acetylcholine and neostigmine results in a graded alteration in the electrical activity of that area of cortex.

When the adenosine triphosphate is applied to the cortex during the excitatory or "convulsive" phase of the acetylcholine response, there is an abolition of the characteristic pattern of spikes induced in the electrocorticogram by acetylcholine.

The suggestion is made that the adenosine triphosphate effect described may indicate that adenosine triphosphate has an anticonvulsant activity. Both the implications of this possibility and those of the effect itself are discussed.

University of Washington Medical Department, Seattle (Dr. Jordan).

2109 Adelbert Road (6), Cleveland (Dr. Badal).

8. Nachmansohn, D.: Chemical Mechanism of Nervous Action, in Currents in Biochemical Research, edited by David E. Green, New York, Interscience, 1946, pp. 335-356.

9. Putnam, T. J., and Merritt, H. H.: Chemistry of Anticonvulsant Drugs, Arch. Neurol. & Psychiat. **45**:505-516 (March) 1941.

ANOXIC ENCEPHALOPATHY FOLLOWING POLIOMYELITIS

Report of a Case

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AND
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IN A RECENT study of bulbar poliomyelitis [1] the conclusion was reached that many of the cerebral symptoms are secondary manifestations of anoxia [2] rather than the result of direct injury to the cortex by the virus. The present paper is a report on the histologic study of a fatal case in which peculiar psychic disturbances resulted from a severe diffuse encephalopathy, ostensibly of anoxic origin.

REPORT OF CASE

Clinical History.—M. P., a girl aged 10 years, was admitted to the pediatric service of the University of Kansas Medical Center (Dr. Herbert Miller), on July 26, 1946. On July 23 she had complained of sore throat and began to have a fever. A local physician gave her sulfonamide drugs, but her fever continued. On July 25 she began to vomit and complained of headache and stiffness of the neck, and her temperature rose to 102 F. (38.9 C.). No muscular weakness was observed.

Past Medical History.—There was a history of pertussis with otitis media (left ear) at the age of 8 months, measles at the age of 3 and 8 years, scarlet fever at the age of 10 years and frequent colds and sore throats, for which the tonsils and adenoids had been removed when she was 5 years old.

There was a family history of diabetes. Of 3 siblings, 1 had rheumatic fever. Another became ill with acute poliomyelitis subsequent to the patient's admission.

Physical Examination.—The child was well nourished and normally developed. The general medical examination showed no abnormality, and there was no lymphadenopathy. Both upper extremities were weak, the weakness being more pronounced on the left and involving chiefly the extensors of the forearms and fingers and the deltoid muscles. The tendon reflexes were all present.

Laboratory Examination.—The initial urinalysis gave normal results. Routine blood counts showed 5,510,000 red cells and 15,150 white cells per cubic millimeter, with a differential white cell count of 79 per cent polymorphonuclear leukocytes,

From the Departments of Neurology and Pediatrics of the University of Kansas School of Medicine.

1. The Bulbar Form of Poliomyelitis: I. Diagnosis and the Correlation of Clinical with Physiologic and Pathologic Manifestations, Minnesota Poliomyelitis Research Commission, J. A. M. A. **134**:757 (June 28) 1947.

2. The term anoxia is used in this paper to mean deficiency in oxygen. Hypoxia would be a more correct term in the physiologic sense.

12 per cent lymphocytes and 9 per cent monocytes. Later blood counts showed little variation from these figures. The reactions to the Wassermann, Kahn, tuberculin and histoplasmin tests were all negative. The spinal fluid contained 875 leukocytes per cubic millimeter, 95 per cent of which were polymorphonuclear leukocytes. The total protein was 48.5 mg. and the sugar 69.2 mg. per hundred cubic centimeters respectively. A second examination of the spinal fluid on July 28, showed 96 leukocytes, 12 per cent polymorphonuclear leukocytes and 88 per cent lymphocytes, per cubic millimeter. The initial chemical determinations on the blood revealed that the nonprotein nitrogen was 43 mg., the creatinine 1.5 mg. and the sugar 87 mg., per hundred cubic centimeters respectively. Cultures of material from the nose and throat and of the spinal fluid and blood yielded no pathogens, but the virus of poliomyelitis was isolated from the stool and transmitted to the monkey in studies by Dr. Herbert Wenner.

Clinical Course.—The child continued to have a temperature between 101 F. (38.3 C.) and 104 F. (40 C.) for the first three days in the hospital. On July 30, or the fourth day in the hospital, she began to have difficulty in breathing, and on the following morning (fifth day) she was placed in a respirator. There she was able to eat and got along well, but at the end of a week (twelfth day) she complained bitterly of pain in the legs and feet, and signs of paralysis developed in the lower extremities. In the meantime, respiratory function was improving. By August 4 she could stay out of the respirator one minute, and by August 6, nine minutes, and by August 10 (fifteenth day) she was able to stay out of the respirator completely. On August 23 (twenty-eighth day) her respirations became gasping, and it was necessary to place her again in the respirator. She became comatose and began to have convulsions, which lasted about an hour. She had minimal respiratory exchange for several hours and remained moribund for approximately twelve hours. Improvement followed the administration of oxygen and fluids. On the return of consciousness she complained of being blind. This lasted twelve hours. After four days in the respirator her condition was greatly improved, and she seemed to have suffered no ill effects from her period of oxygen deprivation. On August 30 (thirty-fifth day) she vomited bile-stained material for about twelve hours. A possible partial intestinal obstruction was considered. A roentgenologic study of the gastrointestinal tract showed that the barium sulfate passed through the small intestine in segments, and not in a smooth flowing fashion. It was suggested by the roentgenologist that this was produced by the effect of the primary disease on the innervation of the intestinal wall.

On September 13 (forty-ninth day) the patient began to vomit during the night, and the following morning she was again found to be cyanotic and comatose. The right pupil was larger than the left, and there was lateral nystagmus. The stomach was distended. Her color and respirations were recorded as "fair" and her pulse as "good." There was a positive Chvostek sign. Blood chemistry studies revealed 50 mg. of nonprotein nitrogen, 1.4 mg. of creatinine, 136 mg. of sugar, 14.5 mg. of serum calcium and 140.4 mg. of serum sodium, per hundred cubic centimeters; the carbon dioxide-combining power was 29.1 volumes per cent in the morning and 46.5 volumes per cent in the afternoon, after the administration of fluids. She was given intravenous injections of plasma, dextrose and calcium gluconate. For the next three or four days she was comatose or delirious but had intervals of lucidity, at which times it was observed that she was blind.

On September 15 the heart rate was slow, with a skipped beat between every three to six beats. An electrocardiogram indicated episodes of complete auriculoventricular block, with absence of ventricular beats. The report (Dr. F. D.

Murphy) follows: "The disturbance in rhythm is basically due to impairment of auriculoventricular conduction, leading to an increased P-R interval, with the addition of Wenckebach's phenomenon. The progressive lengthening of the P-R interval led to complete heart block. The low electromotive force and flat T waves suggest diffuse myocardial undernutrition. The whole picture could be due to prolonged myocardial anoxemia. By September 30 Wenckebach's phenomenon had disappeared, but there was still evidence of heart block of minor grade with delayed auriculoventricular conduction. The RS-T segments are of the type seen in patients with pulmonary disorders."

On September 17 the patient could recognize fingers, but vision was blurred. The optic disks appeared normal. Orientation varied, and she could talk and answer questions but at times was irrational. In neurologic consultation, one of us (A. T. S.) expressed the opinion that the psychic changes were the result of anoxic damage to the brain. Similarity of the symptoms to those observed in postanesthetic encephalopathy was mentioned. On September 19 (fifty-fifth day) the child continued to be irrational, talking or singing continuously. The face, neck and feet were edematous. She complained of pain in her chest and had fever, with temperatures up to 103.6 F. (39.8 C.). There were coarse rhonchi in the apex of the right lung and scattered fine rales over both lung fields. A roentgenogram revealed a patch of pneumonia in the base of the left lung. She was given penicillin, and by September 23 the fever was subsiding and her condition was improved. On September 24 she again appeared pale and seemed poorly oriented; her pupils were dilated, and she could not see. Nystagmus was present. Tapping the cheek or forehead produced contraction of the facial muscles. On September 26 she expressed the fear that snakes were after her. The following day she began to have periodic generalized convulsions. That evening there were clonic twitchings of the abductor muscle groups, the muscles of the mouth and face and the left anterior tibialis. These would become pronounced at intervals, then subside but never disappear. The patient was blind except for light perception the rest of her life. By September 29 (sixty-fifth day) the seizures had stopped, but the child was frequently disoriented and showed memory defects for recent events, with preservation of remote memory. She remained in this condition, and on October 8 it was recorded that she was stuporous a great deal of the time. She also exhibited emotional instability, being easily provoked to laugh or cry. The convulsions did not recur, but muscular twitching about the mouth continued. It was discovered at this time that her blood pressure was greatly elevated, i. e., 180 mm. of mercury systolic and 135 mm. diastolic. Her pulse rate varied from 120 to 140 per minute. On October 26 her temperature rose to 103 F. (39.4 C.) and fluctuated between 103 and 104 F. until death, which occurred on October 27, the ninety-third hospital day. During the last day there were continuous spasms of the lower lip, neck, hips and legs, shallow respiration and profuse diaphoresis.

Clinical Summary: A 10 year old girl with acute poliomyelitis was placed in the respirator on the fifth hospital day because of respiratory difficulty. During the next seven days paralysis of the extremities developed. After ten days the respirator was no longer necessary, but on the twenty-eighth hospital day, after an episode of anoxia, it was necessary again to place the patient in the respirator. After this time she exhibited peculiar psychic and cortical symptoms, consisting of periods of stupor, delirium, labile emotionality, convulsions, clonic muscular twitchings, blindness, disturbed autonomic function of the gastrointestinal tract and heart block. Death occurred about three months after hospitalization.

Autopsy.—Autopsy was performed three hours after her death. The pathologic diagnosis, exclusive of the changes in the central nervous system, was chronic

peribronchitis, atelectasis of the lungs, acute cardiac dilatation, fatty changes in the liver and acute and chronic glomerular nephritis with secondary epithelial calcification.

The brain weighed 1,450 Gm. in the fresh state and 1,330 Gm. after fixation in solution of formaldehyde U. S. P. The leptomeninges appeared edematous. The blood vessels overlying the cortex were moderately hyperemic, and the convolutions were somewhat flattened with shallow sulci. The arteries at the base of the brain were thin walled and collapsed. Coronal section of the brain revealed no ventricular dilatation or gross change except for an area of pale gray discoloration with punctate hemorrhages in the right frontal lobe. The spinal cord appeared hyperemic, and the cut sections showed swelling of the substance of the cord. The gray matter was hemorrhagic and yellow in places. There were marked degeneration and cystic cavitation in the anterior horns at all levels. Poliomyelitis virus could not be isolated from the fresh brain.

Histologic Examination.—Representative areas of the brain and spinal cord were sectioned, embedded in pyroxylin and stained by the Nissl method. Other sections were stained by the following methods: the Braunmühl method for axis-cylinders, various technics for myelin sheaths, scarlet red for fat, the Holzer method for glia fibers and the Hortega method for microglia and oligodendroglia.

Spinal Cord: The leptomeninges were hyperplastic with increase in connective tissue and endothelial cells. There were scattered collections of lymphocytes, especially in the anteromedial fissure.

The degeneration of the anterior horns, amounting in places to cystic degeneration, appeared at all levels of the cord. The anterior horn cells varied in number from loss of certain cell groups to complete absence. At the fourth sacral level the cells of the lateral horn and the anteromedial cell group were absent on one side, and all the ganglion cells but the medial cell group were absent on the opposite side. At the second lumbar level all anterior horn cells were destroyed except for a few in the anteromedial group. The central and lateral areas of the anterior horns were degenerated and cystic. In the lower thoracic portion of the cord (approximately the twelfth thoracic segment) all anterior horn cells were destroyed except for scattered cells in the lateral region of the anterior horn. The cells of Clarke's column were intact. In the lower cervical region most of the anterior horn cells were destroyed (fig. 1). Scattered cells could be seen in the lateral horns and in Stilling's (sacral) nucleus.

The ganglion cells left in the diseased areas varied from those of normal appearance to cells undergoing various types of degeneration. Cells showing acute swelling, cell shadows and shrunken cells were present. There was a striking proliferation of glial cells, both microglial cells and oligodendrocytes. Some phagocytic cells containing brown (blood ?) pigment granules were present. Many of the small blood vessels showed proliferation of both endothelial and perivascular cells. Collections of cells (polyblasts) taking the shape of destroyed ganglion cells were present. Stains for fat showed fat droplets in compound granular phagocytes along degenerating anterior root fibers as they emerged from the ventral funiculus. Fat-filled compound granular cells were scattered uniformly throughout the degenerated anterior horns, without a tendency to collect in the perivascular spaces. Axis-cylinders were thinned out in the anterior horns and thickened in the anterior roots corresponding to the zones which showed a loss of myelinated fibers in the myelin sheath stains. Glial nodes were present in the white matter of the posterior columns in several sections.

Brain Stem: A section through the inferior portion of the medulla showed a patchy area of inflammatory reaction overlying the nucleus ambiguus. The reticular

substance at this level was otherwise spared. At a higher level, circumscribed residual inflammatory lesions were present bilaterally in the reticular substance. They were grossly visible and lay just above the dorsal accessory olivary nucleus on each side (fig. 2). The lesions were similar to those in the anterior horn. There were reduction of ganglion cells, marked proliferation of oligodendrocytes and microglial cells, perivascular collections of inflammatory cells and degenerating ganglion cells. Hortega stains showed many oligodendrocytes and compound

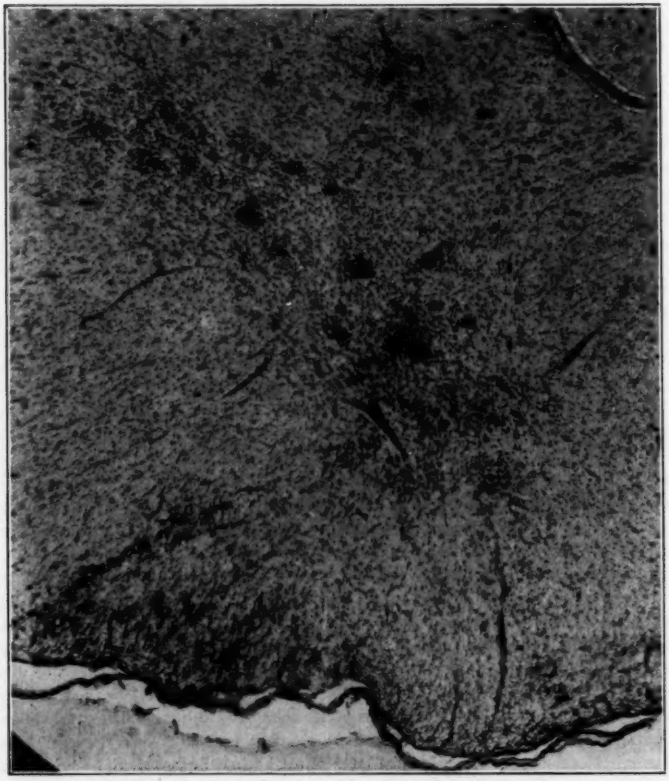

Fig. 1.—Anterior horn of the lower cervical region of the cord, demonstrating the destruction of anterior horn cells and glial proliferation. Nissl stain; × 45.

granular phagocytes. The anterior spinal veins were dilated, and there was perivascular round cell infiltration of the blood vessels along the median raphe. Some ganglion cells of the inferior olivary nuclei were shrunken. Scattered glial nodes could be seen in other parts of the reticular substance. In the pons, scattered, but less pronounced, lesions could be seen in the recticular substance, one lying below the nucleus of the locus caeruleus.

Cerebellum: There were no pathologic changes.

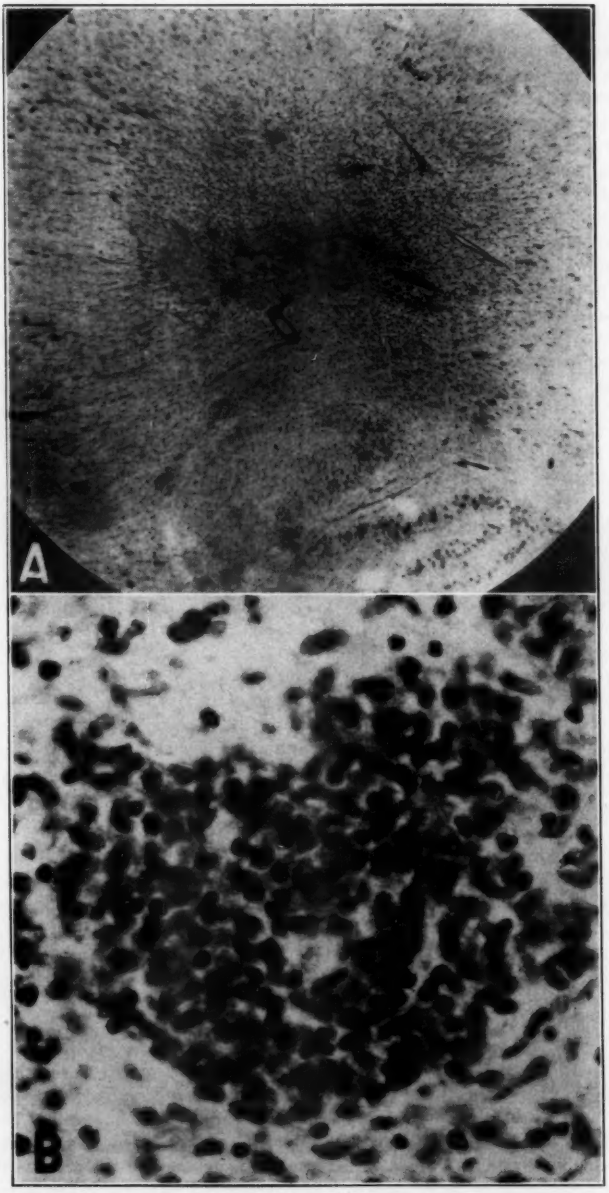

Fig. 2.—*A*, medulla near the summit of the inferior olivary nucleus, with an inflammatory lesion in the reticular substance overlying the dorsal accessory olivary nucleus. Nissl stain; × 20.

B, higher magnification of a portion of the lesion in *A*, showing proliferation of glial cells in an old inflammatory focus. Nissl stain; × 750.

Corpus Striatum: Only slight cellular changes were present. In the caudate nucleus the small ganglion cells had poorly stained cytoplasm and there were numerous cell shadows. In some areas the glial cell matrix showed slight proliferation. Some of the large ganglion cells showed acute swelling and dissolution with numerous glial satellites. In other cells there was perinuclear clearing with the Nissl granules compressed at the cell margin.

Hypothalamus: The subependymal glial cells along the wall of the third ventricle showed regressive changes. The ganglion cells of the nucleus paraventricularis had undergone severe cell disease with vacuolation of the cytoplasm. Other cells showed shrinkage. The cells of the nucleus supraopticus and nucleus tuberalis were swollen and pale with vacuolated cytoplasm. Glial nodes were present in the adjacent white matter.

Cerebral Cortex: The changes in the cortex were of an entirely different character than those of the residual poliomyelitic lesions described in the preceding sections. The changes in the cortex were diffuse and degenerative and varied in intensity from one region to another. This variation was evident even in different parts of a section of one or two convolutions. The severest changes were observed in the frontal pole and the postcentral gyrus. The least damage appeared in the agranular area of the frontal cortex. The hippocampal region was severely involved. The parietal lobe was more involved than the occipital lobe. The estimated degree of severity of involvement of the various areas of the cortex [3] may be tabulated as follows:

Region	Severity of Lesions
Frontal pole (area FE)	+ to ++++
Frontal, intermediate (area FC)	+ to ++
Frontal, agranular (area FB)	+
Precentral (gigantopyramidal cell) (area FAY)	++
Postcentral (area PA_1)	+++ to ++++
Parietal, superior (area PE)	++ to +++
Occipital, area striata and area parastriata (areas OC and OB)	++
Temporal pole (area TG)	+
Hippocampus (areas HE and HE_2)	+++

The leptomeninges in all areas of the cortex were hyperplastic. This change appeared to be greater in the meninges overlying the more severely damaged cortical regions. There was an increase of connective tissue and endothelial cells. Large mononuclear cells and lymphocytes were scattered throughout the tissues. In the postcentral region macrophages were abundant. There were wide dilatation of vascular spaces and moderate thickening of the walls of small arteries in some areas.

In the agranular frontal area the degenerative changes were slight but strikingly uniform. The cytoarchitecture was not distorted, but there was a diffuse, occasionally patchy, dropping out of ganglion cells. This was most apparent in lamina III. The ganglion cells were swollen, with chromatolysis of the Nissl granules. This process of dissolution had advanced to formation of shadow cells. The cells had swollen, pale nuclei and folded nuclear membranes. Neuronophagia was present, especially in lamina V (fig. 3.). Shrunken ganglion cells were scattered here and there. Capillaries were abundant and seemed to have increased in number. The degenerative changes were more pronounced in the depth of the sulci than over the crown of the convolutions. The changes in the ganglion cells were accompanied

3. Areas indicated by the cytoarchitectonic scheme of von Economo.

with an increase of both microglial and macroglial cells. Rod cells were not abundant but became scarcer as zones of greater ganglion cell degeneration and areas of cellular deficit were approached. The rod cells in such areas took on a linear arrangement, radiating from the deeper layers at right angles to the surface.

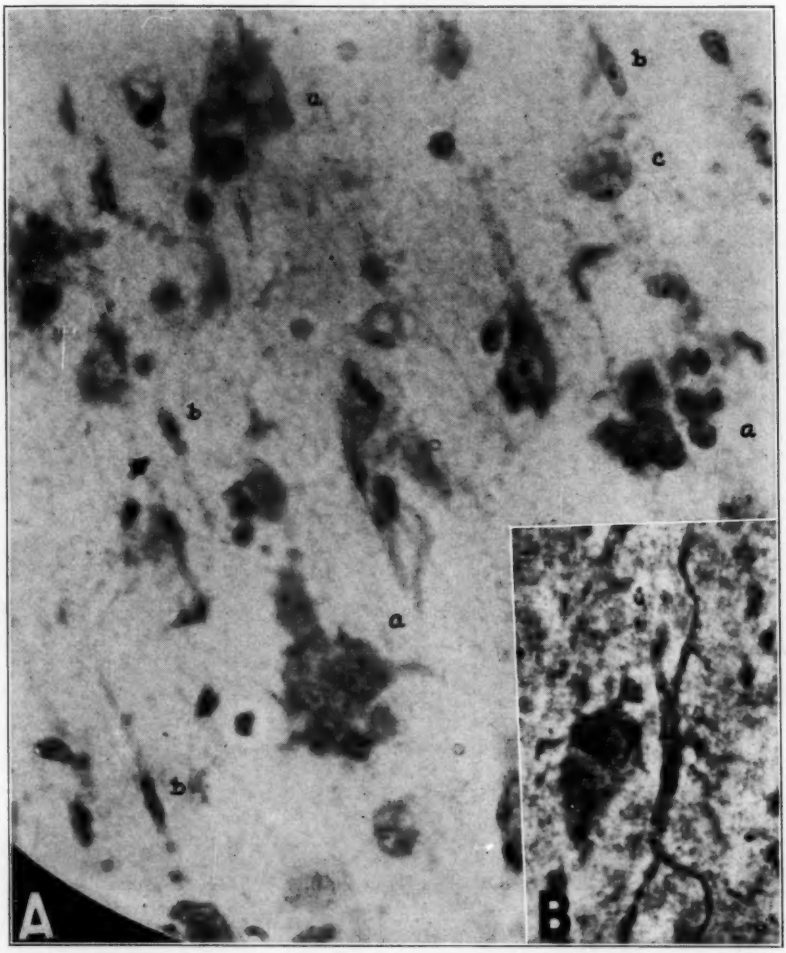

Fig. 3.—Agranular area of the frontal cortex. *A*, degenerative changes: (*a*) neuronophagia, (*b*) rod cell, (*c*) protoplasmic astrocyte. Nissl stain; × 750.
B, section from the same area as that in *A*, showing a rod cell with thickened processes. Hortega stain; × 750.

In more severely diseased areas, such as the frontal pole, the destruction of ganglion cells was severe in all layers (fig. 4). Here the remaining cells showed severe neuronal disease; there were much neurocytophagia and marked proliferation

of both microglia cells and oligodendrogliocytes. Rod cells were abundant, and there was proliferation of capillaries and arterioles, which were surrounded by glial satellite cells. In no place was there any actual perivascular inflammatory reaction. In the subcortical white matter a general increase in glial cell components, glial nodes and perivascular glial satellitosis were evident. The Hortega stain revealed swollen oligodendrogliocytes. Holzer preparations showed moderate marginal glial fibrosis in the molecular layer of the cortex. Fibrillary astrocytes were abundant in the subcortical white matter but were sparse in the other cortical layers. Agonal hemorrhages, not accompanied with proliferative cellular reactions, were present. Regressive changes in the microglial cells were present in the molecular layer of the cortex. Stains for fat revealed no neutral fat in the ganglion cells. There were no componnd granular phagocytes free in the tissues, but they did appear in the Virchow-Robin spaces of some of the blood vessels in the deeper cortical layers and in the subcortical white matter. Sparse fat granules occurred in the glial

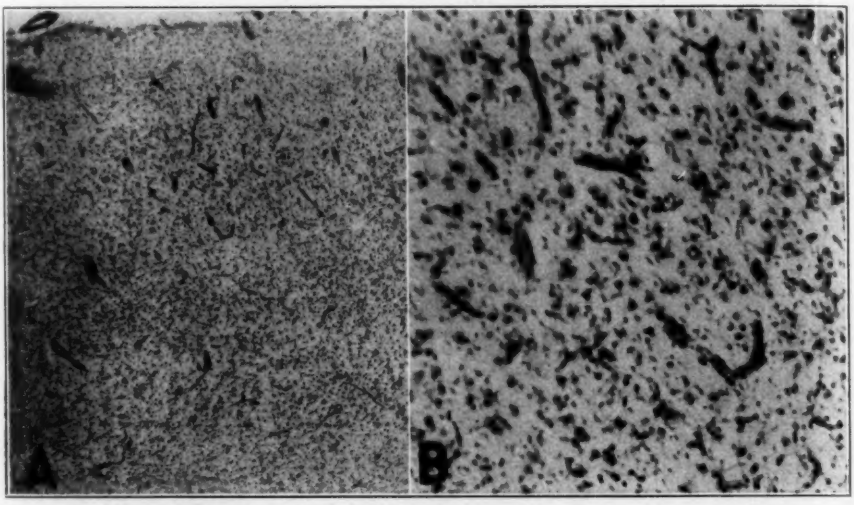

Fig. 4.—Frontal pole. *A*, encephalopathy involving all layers of the cortex. Nissl stain; × 25.

B, higher power showing the marked loss of ganglion cells, accompanied with proliferation of glial cells and capillaries. Nissl stain; × 45.

nodes in the white matter and in the cells adjacent to the capillary walls. No degeneration of myelin sheaths was evident in sections stained by that method. Stains for axis-cylinders showed loss of fibers in the severely degenerated acellular areas, and the radial fibers were scanty in some areas. The ganglion cells present exhibited no intracellular fibrillary degeneration.

Various regions of the cortex showed only different degrees of intensity of the changes described. In the frontal cortex (area FB) neuronophagia was abundant in all layers, but especially in the deeper ones. In the area striata there was greater loss of ganglion cells in the upper three layers. In one area, lamina IV b had also undergone pseudolaminar degeneration. In a section of the area parastriata there was marked proliferation of rod cells in lamina IV b. In the

deeper layers many protoplasmic astrocytes and plump (gemästete) cells were present. Some astrocytes showed mitotic figures, and rod cells were present in all layers (fig. 5). In the postcentral cortex protoplasmic astrocytes were abundant in the upper layers. In many areas Hortega stains revealed hypertrophic microgliocytes, some with processes undergoing clasmatodendrosis. In the precentral (gigantopyramidal cell) gyrus the degeneration was much less severe than in the

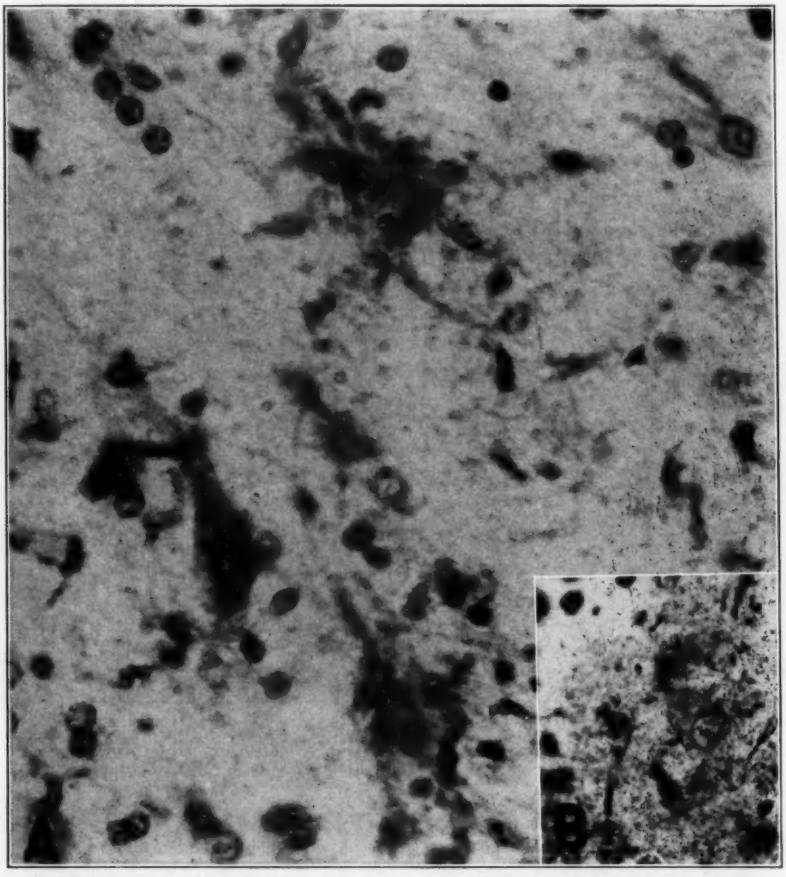

Fig. 5.—*A*, area parastriata, showing ganglion cells with shrunken nuclei. Note neuronophagia and glial cell proliferation. Nissl stain; × 750.

B, area striata, showing protoplasmic astrocytes and the nucleus of a rod cell. Hortega stain; × 750.

postcentral gyrus, lying opposite red on the central sulcus (fig. 6). Cellular loss was marked in lamina III. Microglial satellites (coffin formation) occur around many degenerating ganglion cells. There was loss of Betz cells, and those present showed chromatolysis. Some were seen as shadow cells. One area showed pro-

nounced shrinkage of large pyramidal cells. In others severe cell disease was present. Other ganglion cells showed ischemic neuronal disease with incrustation of the Golgi net. Hortega stain indicated that neuronophagia was by oligodendrogliocytes, some of which were swollen. In the postcentral gyrus the degeneration was pronounced and was greatest in the middle laminas. Pseudolaminar degeneration involved especially the third and fourth layers. In the second layer there were many microglial cells and protoplasmic astrocytes. All ganglion cell layers were degenerated by shrinkage or dissolution, and no normal ganglion cells were present. The cytoarchitecture was disorganized. In one area, laminas III and IV were partially preserved. In the cornu ammonis shrunken ganglion cells and protoplasmic astrocytes were conspicuous. There was loss of ganglion cells in Sommer's sector, and in this area there was rich proliferation of microglial and oligodendroglial cells.

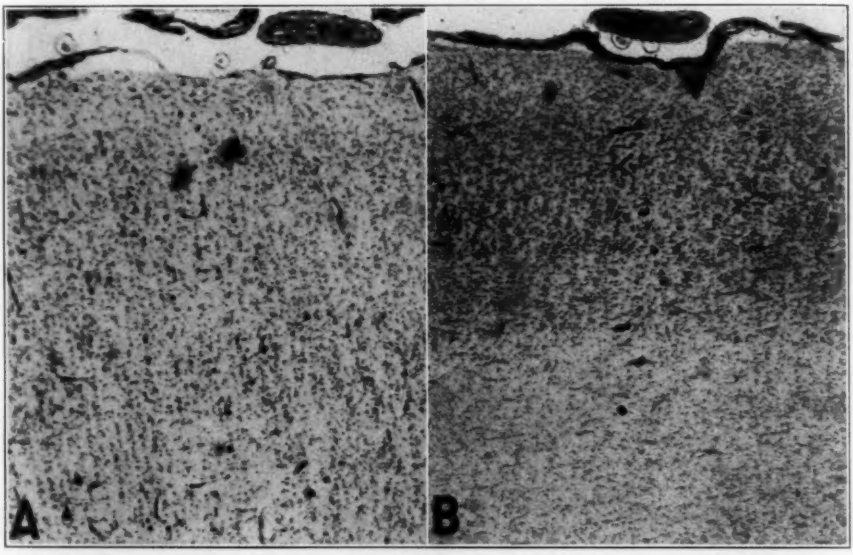

Fig. 6.—Precentral cortex (*A*) and postcentral cortex (*B*), lying opposite each other. The relative position can be seen from the small artery lying in the central sulcus. Note the greater degree of degenerative changes in *B*. Nissl stain; × 25.

The histologic observations may be summarized as follows: The changes in the spinal cord and brain stem were typical of acute anterior poliomyelitis (Heine-Medin disease) in the subacute stage. Degenerative changes in the hypothalamic nuclei were present but were of less certain origin. The cerebral cortex showed a disseminated degenerative encephalopathy characterized by degeneration of the ganglion cells mostly as a result of acute and severe neuronal disease. This destructive process showed marked variation in intensity in different regions but followed the general pattern of pseudolaminar degeneration. There was associated proliferation of neuroglial cells of all types, particularly rod cells and protoplasmic astrocytes. The process was unaccompanied with appreciable demyelination or fatty degenerative changes.

COMMENT

Both clinical and pathologic evidence favors the view that the symptoms exhibited by this patient were of anoxic origin.

The early course of the illness was typical of acute anterior poliomyelitis. Severe embarrassment of respiration developed, so that the child required the aid of the respirator on the fifth hospital day. Within the next few days paralysis of the extremities took place, but within eighteen days after being placed in the respirator she no longer required it. She had become afebrile, had a good appetite and was being treated with hot packs. A minimal return of voluntary muscular movement was present in the right hand and the left leg. During this period she experienced no difficulty in breathing. However, about two weeks after removal from the respirator she was found gasping for breath and was cyanotic and in extreme respiratory distress. She was placed back in the respirator, but, unfortunately, the machine was not working properly and the anoxic period was further prolonged. On being placed in another respirator, she was cyanotic and unable to swallow mucus. In spite of administration of oxygen, she became unconscious and convulsions developed. Recovery was delayed by a period of blindness, which lasted twelve hours.

Disturbance in vision has been observed in postanesthetic encephalopathy (Courville [4]; Steegmann,[5] Löwenberg, Waggoner and Zbinden,[6] and Caine [7]), after anoxia in high altitude flying (Church and Loeser [8]), after removal of a pulmonary embolus (Crafoord [9]) and after anoxia produced by a cervical pressure cuff (Rossen, Kabat and Anderson [10]). It may occur after cortical anoxia produced by any method. The same observers have described other symptoms of anoxic damage to the brain, such as prolonged stupor or unconsciousness, convulsions or muscular twitchings, delirium, hysterical-like behavior and disturbance of autonomic regulation, all of which were exhibited by this patient after the

4. Courville, C. B.: Asphyxia as a Consequence of Nitrous Oxide Anesthesia, Medicine **15**:129 (May) 1936.

5. Steegmann, A. T.: Encephalopathy Following Anesthesia, Arch. Neurol. & Psychiat. **41**:955 (May) 1939.

6. Löwenberg, K.; Waggoner, R. W., and Zbinden, T.: Destruction of the Cerebral Cortex Following Nitrous Oxide–Oxygen Anesthesia, Ann. Surg. **104**:801 (Nov.) 1936.

7. Caine, A. M.: Unusual Complications of Nitrous Oxide–Oxygen Anesthesia, Am. J. Surg. (anesth. supp.) **37**:34 (April) 1923.

8. Church, R. E., and Loeser, L. H.: Injury to the Cerebral Cortex Following Anoxemia and Exsanguination: Report of a Case, Bull. U. S. Army M. Dept., December 1944, no. 83, p. 104.

9. Crafoord, cited by Nystrom, B.: Experiences with Trendelenburg Operation for Pulmonary Embolism, Ann. Surg. **92**:498 (Oct.) 1930.

10. Rossen, R.; Kabat, H., and Anderson, J. P.: Acute Arrest of Cerebral Circulation in Man, Arch. Neurol. & Psychiat. **50**:510 (Nov.) 1943.

period of anoxia. It should also be mentioned that similar symptoms have been observed in experimental animals subjected to anoxia induced by various technics (Oster, Toman and Smith [11]; Morrison,[12] and Weinberger and the Gibbons [13]). The Minnesota group [1] in the poliomyelitis epidemic of 1946 observed psychic symptoms before the appearance of cyanosis. They advocated the use of the oximeter in the detection of early hypoxic states and found that the prompt use of adequate methods to eliminate hypoxia brought about disappearance of the symptoms. It is difficult to determine whether all of the cerebral damage due to anoxia was brought about by the initial episode. Experience with cases of postanesthetic encephalopathy indicate that severe damage may be done by a brief period of anoxia. Since the patient in this case had to remain in the respirator after the initial period of anoxia and was on occasions cyanotic, it is possible that additional minimal periods of hypoxia occurred. The pathologic observations support the idea that the initial period of hypoxia was the most serious one. Later or repeated severe insults would probably have led to the presence of more fat, as shown in the fat stains.

The most important pathologic changes in the organs, other than the central nervous system, were in the heart and kidneys. At autopsy the heart was observed to be acutely dilated. It is not certain whether this was related to the conduction defect, which never disappeared completely. The acute and chronic glomerulonephritis can explain the hypertension observed in the later course of the illness.

The pathologic alterations in the spinal cord and brain stem were typical of the healing stage of poliomyelitis. The pathology of the disease has been thoroughly reviewed and described by Goodpasture,[14] Faber and Silverberg,[15] Luhan [16] and Scheinker.[17]

The bilateral lesions in the reticular formation of the medulla were residua of poliomyelitis. The bulbar and spinal damage to the respiratory

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11. Oster, R. H.; Toman, J. E. P., and Smith, D. C.: Recovery of the Cerebral Cortex of the Cat Following Hypoxia, Am. J. Physiol. **141**:410 (May) 1944.

12. Morrison, L. R.: Histopathologic Effect of Anoxia on the Central Nervous System, Arch. Neurol. & Psychiat. **55**:1 (Jan.) 1946.

13. Weinberger, L. M.; Gibbon, M. H., and Gibbon, J. H., Jr.: Temporary Arrest of the Circulation of the Central Nervous System, Arch. Neurol. & Psychiat. **43**:615 (April) 1940.

14. Goodpasture, E. W., in Infantile Paralysis: A Symposium Delivered at Vanderbilt University, Baltimore, Waverly Press, Inc., 1941, p. 85.

15. Faber, H. K., and Silverberg, R. J.: A Neuropathological Study of Acute Human Poliomyelitis with Special Reference to the Initial Lesion and to Various Potential Portals of Entry, J. Exper. Med. **83**:329 (April 1) 1946.

16. Luhan, J. A.: Epidemic Poliomyelitis: Some Pathologic Observations on Human Material, Arch. Path. **42**:245 (Sept.) 1946.

17. Scheinker, M.: Histopathologic Changes Associated with Human Poliomyelitis, Arch. Neurol. & Psychiat. **57**:565 (May) 1947.

mechanisms in the acute stage unquestionably led to the initial period of anoxia. The Minnesota study [1] led those observers to differentiate bulbar poliomyelitis into a number of types. In some cases the autonomic centers in the medulla were primarily affected; in others the respiratory centers were damaged. This child appeared to have damage to both components; but, in view of the changes in both the hypothalamus and the cerebral cortex, it would be untenable to assume that the bulbar damage was solely responsible for some of the later disturbances of autonomic function. The hypothalamus is frequently the site of inflammatory changes in poliomyelitis (Hechst [18]). It cannot be said with certainty that the residual lesions in the hypothalamus in this case were of poliomyelitic origin. The anatomy of respiratory failure in poliomyelitis has been studied by Finley.[19] Gellhorn [20] has recently pointed out that in chronic anoxia the respiration, and possibly the blood pressure, are regulated through the medullary centers alone. Mild degrees of chronic anoxia may lead to fatal effects if previously damaged medullary neurons are further acted on. This is another reason that administration of oxygen in bulbar poliomyelitis is a rational procedure.

The diffuse degenerative process in the cerebral cortex varied considerably in intensity from area to area. These changes were not similar to those produced by poliomyelitis. Studies already alluded to [21] indicate that the only area of the cortex involved in the acute stage of poliomyelitis is the precentral (gigantopyramidal cell), or motor, cortex, and the pathologic process has the same general microscopic appearance as those in the spinal cord and brain stem. The unusual cerebral manifestations in a case reported by Richter [22] were of obscure origin. He stated the opinion that the process was an associated encephalitis. In Richter's case and in the present one there were inflammatory changes in the area gigantopyramidalis. This was the only area of the cortex showing a real inflammatory reaction; the pathologic process elsewhere seemed to be largely of a degenerative character.

The cortical changes in this case have all been observed before with other types of anoxic encephalopathy. Titrud and Haymaker [23]

18. Hechst, B.: Zur Histopathologie der menschlichen Poliomyelitis acuta anterior, Deutsche Ztschr. f. Nervenh. **137**:1, 1935.

19. Finley, K. H.: The Neuro-Anatomy in Respiratory Failure: Report of Two Cases, Arch. Neurol. & Psychiat. **26**:754 (Oct.) 1931.

20. Gellhorn, E.: The Medulla Oblongata in Anoxia, Arch. Phys. Med. **29**:88 (Feb.) 1948.

21. Goodpasture.[14] Luhan.[16] Scheinker.[17]

22. Richter, R. B.: Acute Anterior Poliomyelitis (Heine-Medin Disease?) with Unusual Cerebral Manifestations, Arch. Neurol. & Psychiat. **42**:1038 (Dec.) 1939.

23. Titrud, L. A., and Haymaker, W.: Cerebral Anoxia from High Altitude Asphyxiation, Arch. Neurol. & Psychiat. **57**:397 (April) 1947.

described hyperplastic changes in the leptomeninges after high altitude asphyxiation. They were observed in postanesthetic encephalopathy by Courville.[4] The degenerative changes in the cortical layers have been noted in cases of cerebral anoxia variously produced. The variation in intensity and the pseudolaminar degeneration are characteristic. The selectivity of the degenerative process for the cerebral cortex and corpus striatum is well recognized, and in severe cases the subcortical white matter undergoes degeneration (O'Brien and Steegmann [24]). The tendency of the degenerative changes to be severest in the cortex at the depths of a sulcus has also been observed in encephalopathy produced by ligation of the carotid artery, i. e., by an ischemic process (Döring [25]). The degree of nerve cell damage varies considerably in different reported cases, as well as in experimental studies,[26] and depends on the degree and duration of the deprivation of oxygen. In anoxic encephalopathy produced by deficiency of oxygen exchange in the lungs, the nerve cell degeneration tends to be diffuse and laminar (actually pseudolaminar) rather than focal. The cell degeneration of Sommer's sector of the cornu ammonis, the presence of ischemic nerve cell changes with incrustation of the Golgi net and the mixture of ganglion cell degeneration due both to swelling and to shrinkage have been reported many times in anoxic states and offer histologic evidence as to the nature of the pathologic process in this case. The hyperplastic changes in the meninges, the vascular proliferation and the remarkable reactions of the neuroglia are all considered secondary reactions to the primary damage to the ganglion cells. The greater vulnerability of the ganglion cells of the cerebral cortex to oxygen lack has been confirmed. Yet there is still a wide gap in knowledge of many factors that are operative in the viability and recoverability of nerve cells subjected to single or multiple and variable degrees of anoxia. In this case the absence of damage to the corpus striatum, the absence of demyelination and the scantiness of fat-filled phagocytes point to the intensity of the original damage rather than to the type of damage.

In any patient who has suffered oxygen deprivation from any cause, the presence of a long period of stupor, visual symptoms, convulsions or muscular twitching, delirium, cerebral excitement or hysterical-like behavior, alternating with stupor and extrapyramidal motor signs, should

24. O'Brien, J. D., and Steegmann, A. T.: Severe Degeneration of the Brain Following Nitrous Oxide–Oxygen Anesthesia, Ann. Surg. **107**:486 (April) 1938.

25. Döring, G.: Zur Histopathologie des Gehirnes bei Spättod nach Erhängen und nach Carotisunterbindung, Virchows Arch. f. path. Anat. **296**:666, 1936.

26. Windle, W. F., and Jensen, A. V.: A Study of the Brain After Intermittent Exposure to a Simulated Altitude of 23,000 Feet, J. Aviation Med. **17**:70 (Feb.) 1946. Grenell, R. G.: Central Nervous System Resistance: Effects of Temporary Arrest of the Cerebral Circulation for a Period of Two to Ten Minutes, J. Neuropath. & Exper. Neurol. **5**:131 (April) 1946. Morrison.[12]

lead the clinician to suspect cerebral damage due to anoxia. There may be associated autonomic disturbances, hyperthermia and increased pressure of the cerebrospinal fluid in individual cases.

In addition, the present case emphasizes the danger in bulbar poliomyelitis of cerebral damage secondary to anoxia. It may be prevented in many cases by the prompt employment of every known aid that will assure the nerve cells a constant supply of oxygen. Atypical and "cerebral types" of poliomyelitis referred to in the older medical literature [27] were usually attributed to effects of the virus on the cerebral cortex. These conditions may really be the aftermath of cortical damage by the anoxic factor during the acute stage, especially when the thoracic or bulbar respiratory mechanism is working inefficiently.

SUMMARY

A 10 year old girl with acute spinal and bulbar poliomyelitis suffered respiratory difficulty. After a period of anoxia evidence of cortical injury developed. This was characterized by stupor interspersed with delirium and hysterical-like behavior, labile emotionality, convulsions and clonic muscular twitchings, blindness and disturbed autonomic function of the gastrointestinal tract. Hypertension and heart block complicated the picture. Death occurred in about three months.

Autopsy revealed acute and chronic glomerular nephritis. The spinal cord and brain stem showed the typical histologic changes of poliomyelitis in the subacute stage. Degeneration of the ganglion cells of the hypothalamus was present. The cortex showed a disseminated degenerative encephalopathy, varying in intensity in different regions but following the general pattern of pseudolaminar degeneration. The damage to the ganglion cells was accompanied with proliferation of the neuroglia, but not by demyelination or mobile compound granular phagocytic cells.

The problem of anoxic encephalopathy is discussed, and the observations in this case are correlated with other types of anoxic degeneration of the brain.

University of Kansas Medical Center.

27. Wilson, S. A. K.: Neurology, edited by A. N. Bruce, Baltimore, Williams & Wilkins Company. 1940, vol. 1, p. 237.

Correspondence

REVIEW OF "DIE MULTIPLE SKLEROSE DES MENSCHEN"

To the Editor:—I wish to protest against the following paragraph of the review of Prof. Georg Schaltenbrand's book entitled "Die multiple Sklerose des Menschen," which appeared in the January 1950 number of the ARCHIVES:

"Chapter 4 contains a critical appraisal of chapter 3, as well as protocols of the author's experiments in man, including his transmission experiments from monkey to man and from man to man. It is regrettable that in his work reported in this chapter the author succumbed to the standards of experimentation on human beings which prevailed in Nazi Germany at that time. In this chapter, Schaltenbrand reports, among similar experiments, what he considered the successful transmission of monkey encephalitis from monkeys to a number of psychiatric patients, listing not only the diagnoses of his victims (they were suffering from various illnesses, including brain tumor, arteriosclerosis and schizophrenia) but also their full first names and the first two or three letters of their family names. A total of 35 names are thus listed. Nothing is said in the book as to whether these patients or their next of kin volunteered for these experiments. The results are unconvincing. Repeated reinoculations were used, and the pathologic changes as described and photographed do not convince this reviewer that anything more than the well known Rivers phenomenon was reproduced."

Even on the basis of chapter 4, as it stands in the book, Professor Schaltenbrand's investigations bear no resemblance to the atrocities committed by physicians in Nazi concentration camps. Dr. A. C. Ivy, Medical Scientific Consultant to the United States Military Tribunal No. 1, Nuremberg, concurs in this opinion. No harm resulted to any patient. In the course of a recent trip to Germany, I was assured that permission had been obtained from the families or, in the case of patients with old schizophrenia, from the responsible head of the hospital to which they had been committed. This is in accord with accepted standards in the use of human subjects in medical experimentation (Ivy, A. C.: *Science* **108**:1 [July 2] 1948).

If Professor Schaltenbrand were guilty of such atrocities, I should be the first to condemn him; but, after careful investigation of the facts by his colleagues, in much more detail and completeness than was possible for me and evidently for the writer of this review, he has been cleared of guilt and restored to his post in the university.

Entirely apart from the question of any possible impropriety of Professor Schaltenbrand's investigations, it seems to me that the insertion of such unrelated gratuitous personal remarks in the appraisal of a scientific work is inexcusable. As an editor, I wish to express my disapproval of such a practice and request that this letter be published in the ARCHIVES.

PERCIVAL BAILEY, M.D., Chicago.

912 South Wood Street.

News and Comment

SEMINAR ON RORSCHACH TESTS

At Michael Reese Hospital Postgraduate School a seminar on the Rorschach test, entitled "The Ego: Growth, Struggle and Decline," will be conducted from June 5 to June 9 by Dr. S. J. Beck, director of the psychology laboratory of the Division of Neuropsychiatry. The inquiry will center on test studies of ego lag in childhood, conflict and breakdowns in the "best" years and losses in the declining years. Differentials in personality structure in these growth phases will be patterned out in the Rorschach test records. Basic test technic will be demonstrated, but the seminar will lay primary accent on interpretation. The course is open to qualified clinical psychiatrists and psychologists. The tuition fee is $50. Further information may be obtained from Dr. Samuel Soskin, dean, Michael Reese Hospital Postgraduate School, Twenty-Ninth Street and Ellis Avenue, Chicago 16.

AMERICAN NEUROLOGICAL ASSOCIATION

The Seventy-Fifth Annual Meeting of the American Neurological Association will be held in Atlantic City, N. J., June 12, 13 and 14, 1950, with headquarters at the Claridge Hotel.

Abstracts from Current Literature

EDITED BY DR. BERNARD J. ALPERS

Anatomy and Embryology

INTERRELATIONSHIP OF THE PARTS OF THE HYPOPHYSIS IN DEVELOPMENT. RAYMOND F. BLOUNT, J. Exper. Zool. **100**:79 (Oct.) 1945.

The epithelial rudiment of the hypophysis was separated from the infundibulum in a series of Amblystoma punctatum embryos. The technic used made it possible to remove the rudiment up to stage 34 (Harrison) without tearing the hypophysial floor.

Transplants of isolated epithelial rudiment alone gave no development of hypophysial tissue. Inclusion of the infundibulum in the transplant resulted in a hypophysis composed of anterior lobe and pars intermedia. If a few cells from the hypophysial floor were included in the graft, a pars intermedia developed. When a block of spinal cord or tail bud separated the epithelial rudiment from the hypophysial floor, the larvae developed with abnormal pigmentation as though hypophysectomized. When the hypophysial floor of the infundibulum was removed with the epithelial rudiment left intact (embryos from stages 24 to 34, and even 36), the larvae showed the pigmentation of the hypophysectomized animal (contracted melanophores and expanded xantholeukophores). Sections showed no pars intermedia. The anterior lobe tissue present was small in amount, deep staining and with pyknotic nuclei. In many cases the thyrotropic activity of the tissue, which was variable, approached the normal, although no metamorphic changes were observed.

The author concludes that the anterior lobe is determined early, at least prior to stage 24. The pars intermedia is not determined before stage 34 but is dependent on the hypophysial floor of the infundibulum.

REID, New Brunswick, N. J.

EFFECTS OF NITROGEN MUSTARD ON EMBRYONIC AMPHIBIAN DEVELOPMENT: I. ECTODERMAL EFFECTS. DIETRICH BODENSTEIN, J. Exper. Zool. **104**:311 (April) 1947.

The effects produced by exposure (forty-five minutes) of larvae of Amblystoma punctatum of various embryonic stages to a 0.001 per cent solution of a nitrogen mustard compound (methyl-*bis*-[2-chloroethyl]-amine hydrochloride) were investigated. Two days after exposure all mitotic activity of ectodermal cells had come to a standstill. The cells were arrested in the interphase state of their mitotic cycle, but the nuclei of these cells continued to grow. The nuclei of cells exposed at earlier stages of development enlarged more than the nuclei of cells exposed at later stages.

After the gradually growing nuclei reached a maximum size, they broke down into fragments of various sizes and numbers. The cytoplasm was not involved in this breakdown. No recovery of nuclei to their active mitotic state was observed. No cellular breakdown occurred in the exposed neural ectoderm.

In the giant cells the number of nucleoli remained at two, indicating their diploid condition. The nucleoli were always enlarged and often fused, giving rise to one

giant nucleolus. Such fusion of nucleoli was also observed in normal cells. The affected cells differentiated normally and gave rise to apparently functional Leydig cells of giant proportions.

In exposed embryos the lateral line primordia retained their power of migration but exhausted their cell material earlier than did the primordia of normal embryos. The differentiated cells of the lateral line organs were unaffected by the chemical, and some of these were observed even in the youngest lateral line organs.

This study emphasizes the highly selective effect of the nitrogen mustard compound on a specific phase of the process of cell multiplication.

REID, New Brunswick, N. J.

RELATION OF THE SPINAL SUBARACHNOID AND PERINEURIAL SPACES. HAROLD M. SOMBERG, J. Neuropath. & Exper. Neurol. **6**:166 (April) 1947.

The existence or absence of direct communications between the spinal subarachnoid and perineurial spaces is yet to be clearly defined. Certain deficiencies exist. First, the experiments should be made on living human material. In addition, the injection medium, in order to pass a minute barrier, must be a true solution and must be nonirritating, in order to prevent phagocytosis. To stimulate physiologic conditions, the pressure at the time of injection must be below 200 mm. of water, and the time interval between injection and observation must be long enough to allow for passage of the substance along a very sluggish circulation.

In order to satisfy these criteria, methylene blue, a nonirritating dye which forms a true solution and is suitable for intravenous use, was injected into the spinal subarachnoid space of 12 subjects who were ill with a non-neurologic disease and had been declared moribund by their attending physicians. In all, 2 cc. of a 1 per cent aqueous solution of methylene blue was injected into the lumbar subarachnoid space after removal of 5 cc. of cerebrospinal fluid. Pressures were taken, and in all cases the readings were below 180 mm. of water. Ten of the patients died, and permission for autopsy was obtained for 6. The 2 patients who, fortunately, recovered, did not show any ill effects from the injections of methylene blue. At autopsy, performed one hour to five days after the intrathecal injection, a complete laminectomy was made in all 6 cases. The spinal ganglia were isolated, and the peripheral nerves up to a distance of 15 cm. were dissected clear. The extent of the blue coloration was carefully observed on both gross inspection and repeated cross-section of the peripheral nerve and ganglion. All observations revealed a constant relation. The blue color, which had filled the spinal subarachnoid space and had dyed the surface of the cord, even the under surface of the dura, stopped at the proximal end of the spinal ganglion. In no instance was there dye beyond this point. Microscopic studies were attempted according to the technic described by Bethe, but the specimens were much too large for adequate precipitation of the methylene blue. Thus, one must conclude that under such physiologic conditions there is no communication between the spinal subarachnoid space and the perineurial space of the spinal nerves beyond the spinal ganglion.

The intrathecal pressure was varied in some experiments. In 3 experiments a pressure of 600 mm. of water was maintained, and after approximately twenty to twenty-five minutes the dye became clearly discernible in the peripheral nerve segment just distal to the ganglion. Thus, under the pathologic condition of increased pressure solutions may enter the perineurial space from the subarachnoid space.

These studies were supplemented with anatomic observations. Serial microscopic sections failed to show any communication of the subarachnoid space with the perineurial space beyond the spinal ganglia, at which point the meninges fused.

GUTTMAN, Wilkes-Barre, Pa.

Physiology and Biochemistry

A Comparison of the Influence of 2,4-Dinitrophenol on the Oxygen Consumption of Rat Brain Slices and Homogenates. C. N. Peiss and J. Field, J. Biol. Chem. **175**:49, 1948.

The oxygen consumption of slices of rat cerebral cortex in Krebs's Ringer-phosphate solution is increased when sufficient 2,4-dinitrophenol is added to the medium to give concentrations ranging from 4.46×10^{-6} to 8.92×10^{-5} molar. Higher concentrations of dinitrophenol depress respiration. Concentrations of dinitrophenol which increase respiration in cerebral cortex slices cause a slight inhibition of oxygen consumption in reenforced brain homogenates. Higher concentrations of dinitrophenol cause more pronounced inhibition. Concentrations of dinitrophenol lower than those increasing respiration in cerebral cortex slices have no effect on respiration of brain homogenates. Concentrations of dinitrophenol evoking a maximum increase in the respiration of cerebral cortex slices bring the oxygen consumption of the slices to about the same level as that in reenforced homogenates untreated with dinitrophenol. It is suggested that increase in cell respiration by dinitrophenol is a matter of "deinhibition" rather than of "stimulation," and that the essential feature of the augmentation is inhibition of an enzyme "brake" or regulator.

Page, Cleveland.

Induced Neurosecretion in Lumbricus Terrestris. Leo A. Schmid, J. Exper. Zool. **104**:365 (April) 1947.

Schmid described the effects of external chemical agents (procaine and epinephrine) on the normal cerebral ganglia of the earthworm, Lumbricus terrestris.

Treatment with procaine significantly increased the number of secreting cells. The granules of these active cells were always rounded and discrete. Worms treated with epinephrine hydrochloride showed a decided increase in the number of secreting cells, but the majority of such cells contained only small granules. Apparently, the epinephrine only initiates the secretory cycle.

A neurosecretory cycle is postulated for the earthworm, since there are noticeable changes in the staining properties of the secretory material and the process of colloid elimination can be readily followed. This cycle is similar to that described by Scharrer in Fundulus heteroclitus.

Reid, New Brunswick, N. J.

The Labyrinthine Reflexes Following Graded Head Trauma in the Rat. Sidney R. Govons, J. Neuropath. & Exper. Neurol. **6**:95 (Jan.) 1947.

Previous studies have indicated that the labyrinths play a greater role in cerebral concussion than has hitherto been suspected. Govons reports preliminary investigations designed to test the labyrinthine reflexes following graded head trauma in the rat.

The technic for the production of trauma to the brain in rats is presented. Cylinders of graded weight were dropped on the animal's head through a steel tube of 2.5 cm. bore. The cylinders were 9.3 cm. in length and 2.0 cm. in diameter and weighed from 5 to 50 Gm. The velocity of the cylinders was controlled by varying the distance through which they were dropped. A sponge, 0.5 cm. thick, placed beneath the jaw of the animal allowed motion of the head.

At least three factors were found to be important in producing an effective mild concussive blow: the weight of the animal, the weight of the striking object and the velocity of the striking object. When these factors are kept constant, repeat-

able effects on the animal can be expected. The exact interplay of these factors in head trauma will form the subject of a future report.

Fifty-four rats, whose ages ranged from 2 to 3 months and whose weight varied from 90 to 120 Gm., were used. A mild type of concussion was consistently produced by dropping a 10 Gm. weight through a distance of 198 cm. on the animal's head. In these circumstances the velocity at impact was calculated to be 621.6 cm. per second. Cylinders of greater weight were also employed, and in those instances the velocity at impact differed; when cylinders of greater weight were employed, a more severe type of injury was consistently produced. A Bárány apparatus for rats was used, and observations were made. The data obtained indicate that in the white rat the labyrinthine reflexes are impaired following the concussive blow to the head. A correlation was observed between the return of "normal" postrotatory nystagmus and recovery from the symptoms following a concussive blow. Preparations are in progress for the study of the effects of graded head trauma in the delabyrinthectomized rat.

GUTTMAN, Wilkes-Barre, Pa.

EXTIRPATION OF THE CORTICAL ARM AREA AS DEFINED BY STIMULATION UNDER CONDITIONS OF PRIMARY FACILITATION (MACACA MULATTA). J. P. MURPHY and ROMAN ARANA, J. Neuropath. & Exper. Neurol. **6**:194 (April) 1947.

Murphy and Arana undertook to compare the motor deficit produced by resection of a somatotopic cortical area with the well known, relatively transient and eventually minimal loss of function which results from extirpation of the area outlined by liminal stimulation and to determine, by restimulation after an appropriate interval of time, whether or not reorganization of cortical function accounted for recovery from paralysis.

The "arm" area, outlined under conditions of primary facilitation, was chosen for extirpation in adolescent monkeys (Macaca mulatta), and the time of observation was approximately eight months.

The authors observed that extirpation of the cortical arm area (Macaca mulatta), as defined under conditions of primary facilitation (stimulation with currents of moderate voltage and high frequency applied to the cortex for ten seconds), resulted in severer and more prolonged deficit of motor power in the contralateral upper extremity than does extirpation of the arm area as outlined by liminal stimulation. The portion of cortex removed from these animals included Vogt's areas 4, 6, 3, 1 and 2.

No evidence of reorganization of cortical function was found on restimulation of the areas of resection and the adjacent cortex eight months later to account for the partial recovery of function in these animals (adolescents).

Removal of the contralateral arm area (an excision of equal size and extent) in 2 animals did not result in a significant further paralysis of the initially paretic upper extremity which could be observed during the time of survival (two days). This suggests the operation of a subcortical mechanism rather than ipsilateral cortical innervation to explain the degree of recovery which did exist.

GUTTMAN, Wilkes-Barre, Pa.

CONVULSANT EFFECTS OF PENICILLIN ON THE CEREBRAL CORTEX. WINSLOW J. BORKOWSKI and FRANCIS M. FORSTER, J. Neuropath. & Exper. Neurol. **6**:201 (April) 1947.

Borkowski and Forster attempted to clarify the nature of convulsive phenomena associated with the administration of penicillin. Experiments were performed on 15 adult cats. Various portions of the cerebral hemispheres were exposed after

the animals had been given diallylbarbituric acid (dial®) with urethane. All applications of the drug were made on filter paper pledgets 1 mm. square. Before applications, excess of the drug was removed by blotting. The concentrations of penicillin used varied from 250 to 10,000 Oxford units per cubic centimeter. The penicillin preparations used were those manufactured by six different commercial corporations.

The studies indicate that penicillin produces discrete high voltage discharges of the cerebral cortex. When these discharges are elicited from the motor cortex, there are corresponding clonic contractions of the represented muscles. Penicillin on application to the cerebral cortex produces electrical discharges, motor disturbances, increased stimulation of both motor and special sensory cortex and a phenomenon of decreased stimulability, probably due to extinction.

Borkowski and Forster conclude that this antibiotic agent should be classified as a convulsant.

GUTTMAN, Wilkes-Barre, Pa.

Neuropathology

CHRONIC PROGRESSIVE SPINO-CEREBELLO-CORTICAL LIPODYSTROPHY AFFECTING CERTAIN ARTERIAL SUPPLY AREAS. OTTO MARBURG and WALTER RIESE, J. Neuropath. & Exper. Neurol. **6**:61 (Jan.) 1947.

Marbury and Riese report the case of a Negro woman aged 29 who had had weakness and ataxia of the legs "almost all of her life." When the patient was 23, weakness and ataxia affecting the upper extremities developed as well. She was unable to write but able to cook and thread a needle. About a month prior to her death she was unable to stand without support. At this time the tremor extended to the head and face. It is stated that the patient's mother, two aunts and an uncle had a similar condition and that the tremor of the patient was more severe on her attempting certain tasks and disappeared during sleep. The patient exhibited more pronounced mental dulness during the last year of her life.

Pertinent neurologic signs at the time of her admission to the hospital were as follows: The patient was semistuporous, and there was a fine constant tremor of the head and the left lower extremity. She had a marked clawfoot on the left and a slight clawfoot on the right. This deformity was associated with a moderate degree of amyotrophy in the lower extremities, more pronounced on the left side. There was no spontaneous movement, and she displayed definite resistance to passive movements. The knee and ankle jerks were absent; the abdominal reflexes were present on both sides. There was conspicuous ataxia in all extremities. Performance in the finger to nose test was defective (dysmetria). There was no nystagmus. In a more lucid period she showed somewhat scanning speech. Her mentality lacked spontaneity and revealed some euphoria. The patient at first had a low temperature, which rose gradually, with occasional spiking. She grew progressively worse and died on April 11, 1944. The clinical diagnosis was Friedreich's disease.

Marburg and Riese call attention to a disease entity the clinical signs of which approach those of Friedreich's disease (ataxia of the legs, absence of tendon reflexes) and which are associated with signs of Marie's disease (cerebellar speech disturbance, intention tremor, absence of Romberg's phenomenon in spite of severe ataxia, tremor, shaking movements), to which are added signs of cortical involvement (epilepsy and mental deterioration, terminating in dementia).

The disease is heredofamilial, with dominant (dominant-recessive) heredity; in other instances it is familial, or even sporadic.

The pathologic changes are progressive degeneration of Goll's funiculus (medial developmental zone), of the border zones of the lateral funiculus and of the cerebellum, with subsequent atrophy of the olivary nuclei and pons, such as seen in olivopontocerebellar atrophy, and, finally, involvement of the cerebral cortex, especially of the frontal lobe.

The sites of the lesions are coincident with areas supplied by certain arteries: the main branches of the truncus arteriosus spinalis posterolateralis and the superior cerebellar and middle cerebral arteries. The spreading of the noxa via the superior cerebellar artery is the cause of the variations in the anatomic picture of the disease, the white matter being in some cases more affected than the gray. As the pons also belongs to the territory supplied by this artery, the simultaneous involvement of the pons and cerebellum is readily explained, whereas the involvement of the olives is retrograde.

The character of the cellular changes in some cases approaches that seen in amaurotic familial idiocy (lipodystrophy). However, other cellular changes occur, depending on the various causative factors. The common factor in these cases is the site of the degeneration, accounting for the identical clinical pictures.

This case belongs with the lipodystrophies and represents a chronic progressive, spinocerebellocortical form.

GUTTMAN, Wilkes-Barre, Pa.

Psychiatry and Psychopathology

ON THE USE OF MENTAL TESTS FOR THE MEASUREMENT OF DISABILITY AFTER HEAD INJURY. GEOFFREY TOOTH, J. Neurol., Neurosurg. & Psychiat. **10**:1 (Feb.) 1947.

Tooth made a statistical analysis of the results of mental tests in a series of patients with closed head injury. The patients were 100 naval officers who were hospitalized with a diagnosis of "postconcussional state." As controls, the author used a group of 50 normal patients, on the one hand, and a group of psychoneurotic patients, on the other, the disturbances comprising hysteria, anxiety and obsessional neuroses. Previous psychologic studies indicated that a difference in retention of early and recently acquired knowledge, as well as an inability to deal with abstractions, was characteristic of organic intellectual disorders. The three groups were subjected to the following four tests: (1) the Wechsler verbal emergency test; (2) Trist's progressive shapes-sorting test; (3) Weigl's color-form-sorting test; (4) Kohs's block test. The results in each group showed that there was no significant difference in the results of the psychologic tests between the patients with head injury and those with psychoneuroses except for moderate impairment in retention and recall of digits and in simple sorting tests. Thus, the difference between the neurotic and the normal groups was just as great as the difference between the patients with head injury and the normal patients. Of the neurotic group, the results for the hysterical personality approached most closely those results for the head injury group, suggesting that a common factor exists in hysteria and the after-effects of head injury. The severity of the head injury was estimated by prolonged post-traumatic amnesia, skull fracture and abnormal neurologic findings. The most severely injured patients gave the most specific type of test pattern. As a possible explanation for the similarity between the results for the patients with head injury and the results for the neurotic patients, the author refers to the observations of Head on the occurrence of primitive reactions which in certain cases accompanied visceral disease. The present studies, in the opinion of the author, are to some extent similar, since in cases of head injury the mental

tests revealed the same primitive mechanism as that which operates in hysteria. In cases of head injury this is probably due to referred pain from as yet unidentified changes within the cranium following head injury.

N. MALAMUD, San Francisco.

PREFRONTAL LOBOTOMY: 1. CLINICAL INVESTIGATIONS OF LOBOTOMIZED PATIENTS. A. MOSOVICH and H. STEVENS, Prensa méd. argent. **34**:1858 (Sept. 26) 1947.

Mosovich and Stevens studied 30 patients who were operated on by Drs. Freeman and Watts at the St. Elizabeths Hospital, Washington, D. C. Patients operated on prior to 1938 were not included because of later changes in surgical technic. Only patients with a postoperative history of six months or more were included. Seven of the patients had been operated on prior to admission to the hospital. Their ages varied from 21 to 70 years, with most between 30 and 50 years of age. The average duration of the psychoses was 10.1 years, and the average period of hospitalization 5.5 years. Only 9 of the 30 patients had been given shock therapy before the operation; 3 had had psychotherapy. For 9 of the patients the diagnosis was dementia precox; for 5, manic-depressive psychosis; for 3, involutional melancholia; for 1, an organic psychosis; for 1, psychosis with cerebral arteriosclerosis, and for 1, a compulsive-obsessive neurosis; 2 had an undiagnosed psychosis. The lobotomies were performed because of the long duration of the illness and the grave prognosis without further treatment; some of the patients were destructive, homicidal and suicidal and were a serious menace. None had responded to other forms of treatment. One patient was agitated, and it was impossible to treat him properly for pulmonary tuberculosis which developed while in the hospital. After the lobotomy he was more accessible and gained weight, and the tuberculosis was controlled. Another patient had lobotomy because of severe lancinating pains due to tabes; he was completely addicted to morphine, and before the operation he was extremely agitated and had suicidal ideas. After the lobotomy the pains were much less severe and responded to ordinary analgesics. The authors mention a patient whose tic douloureux incidentally cleared up after lobotomy for a psychosis. The authors do not concur with the opinion that there is no impairment of intelligence after lobotomy. They believe that the intelligence tests usually used are inadequate and that they are frequently unreliable for psychotic patients, who are often uncooperative. The patients studied had definite impairment of creative thinking; they were unable to make plans of even slight complexity, seemed indifferent about the future and found it difficult to persevere along one line of thought. In at least half the patients there was a definite affective inadequacy after the operation, and even some hypomimia. In 3 patients the death of a near relative produced no significant reaction, not even tearfulness. One patient was euphoric and showed an inappropriate affective response to the bereavement. Ideas and thoughts seemed less frequently emotionally charged; there was oftener a dissociation between affect and ideas or thoughts. The patients became more malleable, passive and less aggressive. They were less affected by competition and reacted less adequately to physical and social stimuli. They were able to adjust at a relatively low level. Egocentricity was frequently noted, as well as superficiality, distractability and the frequent absence of inhibition and self control. None of the patients, however, was guilty of grave antisocial acts or sexual delinquency. A few of the women told of definite diminution of libido. Twenty-one of the 23 patients who had lobotomy benefited from the procedure. Eleven were able to make a social adjustment again; 10 showed improvement; the condition of 1 was unchanged, and that of only 1 became worse.

It is pointed out that, according to Freeman and Watts, these patients continue to show improvement for three years after lobotomy. Rehabilitation of the patients, of course, depends on the level at which they are required to adjust. The patients' age and the duration of the illness seem to bear no relation to the degree of recovery. Ten of the 30 patients had postoperative convulsive seizures, a relatively high percentage as compared with other series of patients with lobotomies. Three patients did not continue to have attacks, even though they were doing without anticonvulsion medication. Six had two or three attacks a year with medication. One patient had petit mal seizures. Five of the 10 patients who had postlobotomy seizures had had electric shock therapy before the operation. Three of the 10 did not improve mentally. The neurologic status was normal in all cases. Postoperative vasomotor phenomena reported by Ziegler were not encountered.

N. Savitsky, New York.

Meninges and Blood Vessels

Modified and Latent Forms of Acute Meningitis and Abscess of Cerebrum in Patients Treated with Penicillin. L. Rouquès, M. David and Jean Pautrat, Presse méd. **56**:194 (March 20) 1948.

Rouquès and his associates point out that acute meningitis and cerebral abscess of patients treated with penicillin often assume modified aspects and may even remain latent. It is not advisable to wait for the appearance of the classic functional signs before considering the existence of these complications. The authors present 2 cases. One concerned acute febrile meningitis manifested only by intense headache, without muscular contracture or changes in the reflexes. The other case was one of a large cerebral abscess with osteomyelitis of the frontal bone; the condition was so dormant that without the existence of papilledema one would have hesitated to affirm the existence of a pathologic process.

J. A. M. A.

Lymphocytic Choriomeningitis (Armstrong's Disease). *B.* Kreis, Semaine d. hôp. de Paris **24**:1018 (April 22) 1948.

Kreis emphasizes that a filtrable virus which was discovered in the United States may be the pathogen in certain forms of lymphocytic meningitis in which recovery occurs. A history of contact with mice, a prodromal febrile period and pronounced hyperleukocytosis of the cerebrospinal fluid aid in the diagnosis. The last-mentioned finding may be further confirmed by animal inoculation or by demonstration of certain reactions of the serum. The virus causes a lymphocytic infiltration of the choroid plexus when inoculated into the brain of mice. Experiments in man revealed that the disease may be reproduced experimentally by the subcutaneous, intramuscular or intravenous injection of 2 cc. of an emulsion of the brain of mice containing the virus; after an incubation period of thirty-six hours to three days a rise in temperature may occur at two or three intervals over a period of up to three weeks, and the last febrile attack may be associated with late meningitic symptoms, such as headache, vomiting and Kernig's sign. In contrast to the tendency of American authors to consider lymphocytic meningitis and choriomeningitis as synonyms, the virus is responsible for only a small number of these cases. The considerable number of persons examined at random whose serum neutralizes the virus suggests that lymphocytic choriomeningitis is to be considered one of the most important infections occasioned by an identified serum.

J. A. M. A.

Diseases of the Brain

PARAPHYSIAL CYSTS OF THE THIRD VENTRICLE. JAMES GREENWOOD JR., J. Neurosurg. **2**:153 (March) 1949.

Greenwood reports 5 cases of paraphysial or colloid cysts of the third ventricle treated surgically. The neurologic symptoms are seldom of localizing value. Ventriculography shows lack of filling of the third ventricle, but the air may occasionally outline the tumor. Three operative approaches to the third ventricle may be used: (1) through the posterior portion of the corpus callosum, (2) through the anterior portion of the corpus callosum and (3) a transcortical route. The last is easiest but may lead to postoperative convulsions.

The author's operative results were as follows: one death, with 2 of the 4 survivors able to work. All 4 patients have had one or more convulsions since the operation, and 1 of the 4 died seven years after the operation, at the age of 63, with severe mental deterioration.

Greenwood believes that emergency ventriculography is mandatory in cases of rapid, unexplained coma if there have been similar previous attacks.

TOZER, Philadelphia.

DISSOCIATION OF PHONETIC ALTERATIONS WITH A RELATIVE PRESERVATION OF THE OLDER LANGUAGE IN A BILINGUAL FRENCH PATIENT WITH PURE ANARTHRIA. T. ALAJOUANINE, P. PICHOT and M. DURAND, Encéphale **38**:245, 1949.

The authors report the case of a white man, aged 63, who had suffered a right hemiplegia, due to hypertension and arteriosclerosis. The patient was French born, of a French father and English mother. He had known only English up to the age of 3 or 4 years. He had been, before the accident, completely bilingual, with a perfect mastery of both tongues. Although many have disputed the idea of a pure anarthria apart from aphasia, the authors state the belief that at the time they studied the case all elements of aphasia which might have existed previously had disappeared. Their detailed psychologic protocols bear this out. They believe that it is incorrect to think that the more refined the psychologic studies of such cases, the more do cases of pure anarthria disappear.

The second conclusion of the paper is based on elaborate and careful study of the graphic registration of the patient's speech. This type of study revealed that the same phoneme was pronounced correctly or incorrectly, depending on whether it was part of an English or a French word. If it was part of a French word, it was incorrectly pronounced. They believe that the results of this study bear out conclusions of the same nature as those made in earlier studies in which they found a special phonetic dissociation syndrome and in which articulatory disturbances were independent of the total *ensemble* of aphasic disturbances in certain patients. The patient, the subject of the present paper, showed clearly that a given phoneme or group of consonants whose pronunciation in French was very defective was perfectly pronounced in English words. In short, the more "primitive," earlier learned, language was much less altered than the more recently acquired one, in accordance with Jackson's doctrine. The dissociation could hardly be a question of motor disturbance, since the phonemes are pronounced the same in the two languages. The trouble lies in the "cohesion," or dynamic assembly of the elocution. This is at a level far higher than that of simple motor activity. The dissociation must take place at a higher articulatory level; such a dissociation is completely incomprehensible at the purely motor level.

ZINKIN, New York.

IMPAIRMENT OF FUNCTION OF THE LEVATOR PALPEBRAE MUSCLE ASSOCIATED WITH A HERTWIG-MAGENDIE SYNDROME. FRIBOURG-BLANC, CHARLIN, HECAEN and ROZAN, Rev. neurol. **77**:34 (Jan.-Feb.) 1945.

A man aged 34 was struck over the right eyebrow by a piece of cement six months prior to examination. He was dazed. During the next few days he noted drooping of the right upper lid and retraction of the left upper lid. When the right eye was closed, the retraction disappeared. Examination revealed ptosis of the right upper lid and retraction of the left upper lid. There was no compensatory wrinkling of the frontalis muscle. On his looking downward, the left eyeball deviated upward and the right eye downward. Blinking was perhaps less frequent than normal. There was normal reflex response of the lids to threat of injury, the reaction on the right being perhaps somewhat less than that on the left. There was only slight elevation of the right upper lid with the help of the frontalis muscle. The left lid showed very slight movement, owing to retraction. On his looking downward, the left upper lid lagged, and on his looking upward, the left upper lid readily reached its maximal elevation. There were normal associated movements of the right upper lid on looking downward. The corneal reflexes were intact; there was no exophthalmos. The pupils were equal and regular and reacted well to light and in accommodation. Procaine injected into the temporo-supraorbital region had no effect. The instillation of cocaine caused slight retraction of the upper lid and mydriasis on the right; on the left there was mydriasis with no effect on the lid. Labyrinthine tests gave normal results. Visual acuity, the visual fields and the fundi were normal. Electrical reactions of the muscles of the lids were normal. A roentgenogram of the skull showed nothing abnormal. The neostigmine test gave a negative result. The authors note the minimal nature of the trauma, which probably caused a small hemorrhage in the region of the cerebral peduncle. One lesion probably produced ptosis on one side and retraction of the opposite lid. In their opinion the associated Hertwig-Magendie syndrome was due to another lesion, in the region of the posterior longitudinal bundle. The patient later showed some spontaneous improvement.

SAVITSKY, New York.

HEREDITY OF STURGE-WEBER-KRABBE DISEASE. DENISE LOUIS-BAR, Confinia neurol. **7**:238, 1947.

Louis-Bar reviews the literature on Sturge-Weber-Krabbe disease (cutaneous vascular nevi in a trigeminal distribution associated with intracranial angiomas) and finds it wanting in enough evidence to permit consideration of the disease as a hereditary process. A case is reported in which a grandmother and grandson both had vascular nevi in the distribution of the third branch of the trigeminal nerve. Autopsy on the grandmother revealed no intracranial angioma, and clinical and roentgenologic examinations of the grandson likewise revealed no such lesion. In view of the great frequency of the cutaneous manifestations of this disease, the author regards this case only as an interesting coincidence.

FOLEY, Boston.

RH INCOMPATIBILITY AND MENTAL DISEASE (ENCEPHALOPATHIES AND OLIGOPHRENIAS). MANUEL FRANCISCO BECA, Rev. de psiquiat. **11**:51, 1946.

Beca reports 5 cases of double athetosis with mental deficiency. In 1 case there was also spastic tetraplegia, and in another there were cerebellar signs. In each case the mother was Rh negative and the child Rh positive. In 2 cases there was a suggestive history of erythroblastosis in the children, and in 1 case, a familial history of erythroblastosis.

N. SAVITSY, New York.

HYDROCEPHALUS AS A LATE SEQUELA OF RUPTURED BASILAR ANEURYSM. H. KRAYENBÜHL and F. LÜTHY, Schweiz. Arch. f. Neurol. u. Psychiat. **61**:7, 1948.

There is little in the literature regarding the ultimate fate of persons who survive rupture of an intracranial aneurysm. The first of 2 patients whose cases are reported, a woman aged 52, awakened with right hemiparesis and motor aphasia twelve days after the onset of subarachnoid hemorrhage. A saccular aneurysm of the anterior communicating artery near its junction with the left anterior cerebral artery was demonstrated by arteriography, pneumoencephalography performed by the cisternal route having revealed a normal ventricular system. The patient's husband refused to permit ligation of the left common carotid artery. Symptoms of meningeal irritation subsided, but later paralysis of the right extremities became complete and the severe headache recurred. Ten months after the first examination, pneumoencephalography performed by the combined cisternal and lumbar routes disclosed internal and external hydrocephalus with a relatively greater degree of dilatation of the anterior horn and pars centralis of the left lateral ventricle. Nearly fifteen months after onset, the left frontal lobe was exposed by means of an osteoplastic flap and drainage of the lateral ventricle established by removal of a generous piece of brain substance. Microscopic examination of the tissue revealed evidence of old and recent hemorrhage in the leptomeninges with extensive fibrosis and formation of cysts. Of particular interest was strangulation of some of the pial veins by thick rings of hyaline connective tissue. Sections from the cortex showed areas of softening, focal degeneration of ganglion cells and an accumulation of granular cells containing fat. The patient's condition improved after operation but later became worse, and she died thirty months after onset of hemorrhage. Autopsy revealed a high grade internal hydrocephalus, which was more pronounced on the left side, and areas of softening in both hemispheres. Evidence of a healed rupture was observed in one of two small aneurysms involving the anterior communicating artery.

The second patient, a man aged 38, apparently experienced five recurrent subarachnoid hemorrhages over a period of seventeen months preceding his admission to the hospital. Edema of the right optic disk with peripapillary hemorrhages and hyperactivity of the knee and ankle jerks on the same side were noted on examination. Ventriculographic studies revealed a moderate degree of internal hydrocephalus, which was evidently of the communicating type, since the fourth ventricle contained air. After an aneurysm of the anterior communicating artery was demonstrated by arteriography, the left common and external carotid arteries were ligated, along with the left superior thyroid artery. The patient recovered and was free of symptoms when reexamined two months after operation.

In their discussion, the authors state that the foramens of Luschka and Magendie were open in the first case. To their surprise, the pacchionian granulations were entirely normal, being in fact the only leptomeningeal structures which did not contain iron. They express the view that in both cases the channels for escape of cerebrospinal fluid were restricted by fibrosis of the leptomeninges to the degree that hydrocephalus male resorptivus resulted.

DANIELS, Denver.

TETANIC SYNDROME WITHOUT CHANGE IN BLOOD CHEMISTRY APPEARING IN JUVENILE DEMENTIA PARALYTICA. L. VAN BOGAERT, Monatsschr. f. Psychiat. u. Neurol. **118**:30 (July) 1949.

Van Bogaert reports the case of a boy aged 13 who was stricken with juvenile dementia paralytica and whose father was hospitalized with the adult form of the

disease. Clinically, he presented pupillary changes, cerebellar signs, speech disturbance of a dysarthric nature and visual diminution, culminating in blindness due to bilateral optic nerve atrophy. He gradually became bedridden, and quadriplegia in flexion developed. He was also subject to epileptic seizures. During a three year period of progression of his illness, opisthotonos and carpal spasm were observed, the least touch precipitating generalized muscular hypertonia. The cramps produced by the manipulation of his extremities were painful, and his face assumed a sardonic smile. The Chvostek and Trousseau signs were positive on both sides. The calcium and phosphorus levels of the blood were not elevated. The Wassermann reactions of the blood and the spinal fluid were positive, with an increase in the cells and protein of the spinal fluid. Deglutition became difficult, so that the patient had to be tube fed. During the terminal period there was marked contracture of the extremities, with exaggeration to tactile stimulation.

Pathologically, there was no evidence of parathyroid disease. The brain showed evidence of meningeal thickening and generalized atrophy. The cortex showed extensive cellular changes of the Lissauer type. Histologically, of interest was the presence of pseudocalcific deposits both in the parenchyma and along the vessels, particularly of the putamen, thalamus and pallidum. These lesions resembled the "idiopathic perivascular calcification" of Fahr. Strangely, in the areas showing this alteration there was no evidence of the spongy state or of serous imbibition of the tissues.

PISETSKY, New York.

AN ELECTROENCEPHALOGRAPHICALLY LOCALIZED FOCUS IN A CASE OF THE STURGE-WEBER SYNDROME, EXTIRPATED WITH GOOD RESULT. B. BROAGER and H. HERTZ, Acta psychiat. et neurol. **24**:1, 1949.

More recent studies on the Sturge-Weber syndrome, which consists of unilateral facial nevi with cortical calcification and unilateral or bilateral seizures, indicate that the calcifications seen in the roentgenogram are due to deposits of calcium in the atrophic cortex, rather than to calcified blood vessels. The atrophy is more extensive than would appear from the extent of the calcifications in roentgenograms. Air studies demonstrate diffuse atrophy. The convulsions begin in childhood and are difficult to control. They may be unilateral but present no other localizing characteristics. In the case reported, the site of the calcium deposits did not correspond to the epileptogenic focus. A 5 year old girl with nevus flammeus of the left side of the forehead, nose and upper lip had had epileptic seizures since the age of 1 year. The convulsions started in the right arm and right leg and, despite phenobarbital medication, occurred at the rate of ten seizures a day. Roentgenograms of the skull indicated typical tortuous calcifications in the left occipital region, and air studies showed cortical atrophy, more pronounced on the left. Electroencephalograms showed diffuse spike and wave patterns over the entire cortex, and there was a parasagittal premotor focus with constant phase reversals. Extra electrodes helped in determining the focus more precisely. At operation, the left premotor area was exposed, a nevus on the inside of the dura was coagulated and block resection of the entire parasagittal premotor area was carried out. Temporary right hemiparesis followed. An electroencephalogram one week after operation exhibited diffuse slow waves over the entire cortex, with no other alterations. During the subsequent year, under a regimen of diphenylhydantoin and phenobarbital, the patient had had no seizures.

J. PISETSKY, New York.

Diseases of the Spinal Cord

SYNDROME OF NEUROMYELITIS OPTICA: A CASE REPORT WITH NECROPSY FINDINGS. C. H. ARMENTROUT and E. D. PEASLEY, Ann. Int. Med. **32**:129 (Jan.) 1950.

The case reported presents the clinical syndrome which has been described as neuromyelitis optica, or Devic's disease, characterized here by a rather acute onset with initial symptoms referable to the spinal cord, followed by signs of involvement of the optic nerve. The involvement of the spinal cord was initiated by sensory changes in the lower limbs, followed in approximately three weeks by signs of involvement of the optic tract, which progressed in three days to almost complete amaurosis. The disease process in the spinal cord, which first produced only sensory changes, advanced rather rapidly and presented the picture of complete transection of the cord, with bilateral paralysis, total sensory loss and absence of sphincter control. There was a rather rapid progression upward, with signs of involvement of the lumbar, dorsal and cervical segments of the spinal cord, with death as the result of bulbar paralysis.

The necropsy findings were those of a diffuse demyelinating process of the spinal cord, with areas of softening and cavitation accompanied with a strong phagocytic reaction. Some areas showed a perivascular lymphocytic infiltration, but there was no evidence of glial proliferation. In addition, the right cerebral hemisphere showed three sharply circumscribed areas of demyelination with a marked phagocytic reaction and without gliosis.

Microscopic sections taken from the optic nerves and the postchiasmal portions of the tracts showed no evidence of degeneration. The eyes were not examined.

ALPERS, Philadelphia.

CERVICAL EPIDURAL ABSCESS. D. G. LACOSTA, Brasil med. cir. **8**:85 (April-Aug.) 1946.

Three months prior to hospitalization, a man aged 44 complained of pain in the region of the left scapula. A few days after the onset, the pain became worse, and his temperature rose to 40 C. (104 F.), remaining elevated for about twenty-five days. Soon after the onset the pain began to radiate to the left arm and at times down both legs. The pain was made definitely worse with movement. The patient was given large doses of penicillin, but his general condition became worse. Three weeks before his admission weakness in the lower limbs appeared, more pronounced on the left. The left upper limb also became weak. Movements of the arms intensified the pain. He began to have trouble with urination. There was no response to antisyphilitic treatment, though the blood and spinal fluid gave positive reactions for syphilis. Myelographic studies showed complete block at the sixth cervical segment. The patient was admitted to the hospital, emaciated, pale, dehydrated and almost cachectic. There was severe pain, especially in the region of the left scapula and the left upper limb. The temperature rose every evening; the pulse rate was 94, and the blood pressure 115 systolic and 65 diastolic. Examination showed Horner's syndrome and marked weakness of the upper and lower limbs on the left side; less marked weakness of the right lower limb; hyperreflexia on the right side, and a sensory level at the first thoracic dermatome. A blood count showed 10,000 white cells with a large percentage of polymorphonuclear leukocytes. A second myelogram again showed block at the sixth cervical segment. The laminas of the fifth to the eighth cervical vertebrae inclusive were removed four days after his admission. The dura was thickened, and at the sixth and seventh cervical level there was green pus (Staphylococcus aureus). The

patient showed improvement after twenty days, when analgesics were no longer necessary. He was able to walk after three months. The Horner syndrome disappeared. He was given sulfonamides, penicillin and antisyphilitic treatment after operation. The myelogram taken soon after the operation no longer showed block. One month prior to the onset of the illness the patient had had infected bruises of the lower limbs.

N. SAVITSKY, New York.

Vegetative and Endocrine Systems

PATHOGENESIS OF PROGRESSIVE CEPHALOTHORACIC LIPODYSTROPHY. LUIS BARRAQUER FERRÉ, J. Nerv. & Ment. Dis. **2**:113 (Feb.) 1949.

This disease is characterized by the absence of fat tissue in the face, arms and trunk, in contrast to normal or pathologic accumulation of fat tissue in the inferior half of the body. The author reviews the literature and states the belief that both a heredodegenerative and a secondary form are due to a degeneration of the highest trophic centers of the hypothalamus. This destruction causes hyperactivity of the vegetative centers, especially in the cervical sympathetic chain, and consequent loss of the subcutaneous and fat tissue. The author reports a case in which the disease was hereditary in three generations.

FARMER, Philadelphia.

NERVOUS CACHEXIA AND SIMMONDS' DISEASE. ROMULO REPETTO, JUAN IANNI and ISAAC BENZECRY, Arq. clín. **2**:265 (May) 1946.

The authors report the case of a girl aged 17 who was first seen because of persistent anorexia, asthenia and loss of weight. Soon after the onset of the illness in the middle of 1943, she weighed 82 Kg. After discussing her weight with a young man who tried to lift her but could not, she became very much disturbed. The thought of his inability to lift her became an obsession. She went on a diet and for a while took only twelve lemons a day. When ready to stop dieting, she found she had no appetite and continued to lose weight. When seen on first examination, she weighed 50.4 Kg. Her blood pressure was normal. Her menstrual periods stopped after November 1943. The blood sugar during January 1944 was 82 mg., and the blood urea 30 mg., per hundred cubic centimeters; the basal metabolic rate was —12 per cent. She responded only temporarily to treatment. Anorexia, nausea, vomiting, insomnia and emotional lability persisted. On readmission in July 1945, she weighed 32 Kg. Her basal metabolic rate was —36 per cent; the sugar tolerance curve showed a fasting sugar of 54 mg., with 76 mg. after one hour, 57 mg. after two hours and 45 mg. after three hours. The electrocardiogram was normal. Urinary 17-ketosteroids were absent; none was found in a twenty-four hour specimen of urine. The authors believe that in this instance anorexia nervosa developed into Simmonds' disease. The absence of 17-ketosteroids in the urine and the low blood sugar indicate the presence of Simmonds' cachexia. The progressive lowering of the basal metabolism also indicates such an evolution. The authors do not believe that the appearance of amenorrhea during the course of anorexia nervosa indicates its transformation into hypophysial cachexia.

SAVITSKY, New York.

ETIOLOGY AND PATHOGENESIS OF CEPHALOTHORACIC LIPODYSTROPHY. L. BARRAQUER FERRE and J. JIMENEZ VARGAS, Med. clin. **6**:1 (Jan.) 1946.

The syndrome of progressive cephalothoracic lipodystrophy, or Barraquer's disease, is characterized by the absence of fat from the subcutaneous tissues of the face, upper extremities and upper half of the trunk. There is present a normal,

or excessive, amount of fat in the lower half of the trunk, especially over the buttocks, and the lower extremities. Barraquer's disease is present in two forms: genuine and symptomatic. The genuine form is caused by a heredodegeneration, that is, a progressive dysbiotrophy of the hypothalamus due to genotypic factors. The symptomatic form may have non-neurogenic factors, such as hormonal dysfunction, or neurogenic causes, either peripheral or central, such as encephalitis.

The authors base their study on 10 cases, in 1 of which the disease was transmitted to the third generation.

ABOLOFIA, Philadelphia.

SYNDROME OF ACHARD-THIERS. A. TACHELLA COSTA, E. DEL ZAR and R. REPETTO, Rev. Asoc. med. argent. **59**:1153 (Oct. 15) 1945.

The nineteenth case of the Achard-Thiers syndrome is reported (*Bull. Acad. de méd., Paris* **86**:51, 1921), that of a woman aged 32 with virilism and diabetes mellitus. There was a history of hypomenorrhea for two years. The present illness began a few months before the patient was seen by the authors, with frontal headaches and diminution of vision. Polydipsia, polyuria, hyperhidrosis, anxiety, pain in the trunk, especially on the right side, and rapid appearance of hair on the face were noted. There were also a rapid pulse and palpitation. Amenorrhea had been present for one month. Examination showed diminished vision with neuroretinitis, hair on the face with a mustache and beard, diffuse enlargement of the thyroid gland, atrophic mammae, a blood pressure of 200 systolic and 120 diastolic, a pulse rate of 120, a soft murmur over the pulmonic area, a palpable, tender right kidney, fine tremors of the extended fingers and red cyanosis of the extremities. The Wassermann and Kahn reactions of the blood were negative. The sugar content of the urine was 12.37 per cent; the blood sugar measured 70 mg. [sic.] and the urea 40 mg. per hundred cubic centimeters. The concentration tests gave normal results; venous pressure was 19 cm.; circulation time, thirteen seconds; vital capacity, 2,500 cc., and basal metabolic rate + 51 per cent. There was an increase of 17-ketosteroids in the urine (51.7 mg. in twenty-four hours). Tumor of the right adrenal gland was demonstrated with perirenal insufflation, according to the technic of Carelli and Sordelli. The authors emphasize the differentiation of the Archard-Thiers syndrome and the Cushing syndrome. Excretion of androgens in the urine is normal in the Cushing syndrome. They also note the frequency with which disorders of other glands are associated with the Achard-Thiers syndrome. In this case hyperthyroidism was present. Preparations were made for surgical intervention, but the patient left the hospital. She died later, and necropsy was not obtained.

SAVITSKY, New York.

Treatment, Neurosurgery

MEDULLARY TRACTOTOMY FOR RELIEF OF INTRACTABLE PAIN IN UPPER LEVELS. ALBERT S. CRAWFORD, Arch. Surg. **55**:523 (Nov.) 1947.

Satisfactory relief of intractable pain in the upper extremities and the cervical and shoulder areas can be obtained by medullary tractotomy. Crawford sectioned the lateral spinothalamic tract approximately 5 mm. caudad to the level of the obex, carrying the incision to a depth of 5 mm. The operation, performed with use of local anesthesia and with the patient in the sitting position, was unilateral in 9 patients and bilateral in 2 patients. Both patients with bilateral tractotomy and 1 of the patients with unilateral tractotomy died after operation, of respiratory paralysis. A high level of analgesia, varying from the second to the fourth cervical segment, was obtained in all cases. There was transient ipsilateral hemiparesis in 5 cases.

LIST, Grand Rapids, Mich.

REPAIR OF DEFECTS IN ETHMOID AND FRONTAL SINUSES RESULTING IN CEREBROSPINAL RHINORRHEA. ALFRED W. ADSON and ALFRED UIHLEIN, Arch. Surg. **58**:623 (May) 1949.

Cerebrospinal rhinorrhea is commonly caused by basal skull fracture, but the condition may develop spontaneously as a result of congenital defect in the cribriform plate. Finally it may follow the removal of nasal polyps associated with nasal meningocele. Cerebrospinal rhinorrhea can be differentiated from vasomotor rhinitis by subarachnoid introduction of a dye (indigo carmine), which stains the nasal discharge. Meningitis is a dreaded complication of the rhinorrhea, particularly in the presence of infection of the upper respiratory tract. In cases of acute rhinorrhea following skull fracture, it is always advisable to follow at first a conservative course of approximately eight weeks before attempting surgical closure of the leak. In most cases the discharge of cerebrospinal fluid ceases spontaneously. Chronic rhinorrhea, however, requires surgical repair, since palliative measures, such as application of silver nitrate solution, are rarely effective. Attempts to close the fistulous opening(s) through a unilateral frontal craniotomy often have been disappointing, especially when multitude defects were present in the cribriform plate. Adson prefers a bilateral extradural frontal approach with ligation of the anterior part of the superior longitudinal sinus. The variety of operative findings precludes routine management but requires an individual surgical approach. Smaller defects in the bony wall of the paranasal sinuses are occluded with bone wax. Larger defects are covered by gelfoam,® polythene film or animal membrane or by a tantalum plate. If possible, the dural tear should be closed by inverting sutures. Administration of penicillin and sulfonamides in the preoperative and postoperative periods serves as a protective measure against the hazard of meningitis. In the series of the Mayo Clinic, 26 patients with cerebrospinal rhinorrhea were operated on. In 8 cases the condition was caused by trauma; in 18 others it was nontraumatic and spontaneous in origin. Most commonly, the fistulous opening led into the ethmoid cavities (21 cases). Twenty-two of the patients were cured by the operation. In 1 case the result was equivocal, and in the remaining 3 the condition was not relieved by the operation. There were no surgical deaths.

LIST, Grand Rapids, Mich.

TREATMENT OF ALCOHOLISM WITH ANTABUS. ERIK JACOBSEN and O. MARTENSEN-LARSEN, J. A. M. A. **139**:918-922 (April 2) 1949.

During experiments performed with tetraethylthiuram disulfide (antabus®) in the laboratory, it was discovered that persons who have ingested this substance showed symptoms after consumption of alcohol which differed quantitatively and qualitatively from the common picture of alcoholic intoxication. The present report includes a short review of the results obtained in the investigation on the biochemical mechanism of this effect and of the clinical results in 100 persons with alcoholism who were treated for six to twelve months.

Tetraethylthiuram disulfide is a white or slightly yellowish powder, which is insoluble in water. It is relatively nontoxic. When a human subject has taken the drug twelve hours previously, the ingestion of alcohol is followed shortly by an intense feeling of heat in the face, and then vasodilatation of the face, neck and scleras, with perhaps edema about the eyes. The pulse rate is increased to 120 or 140; the blood pressure is unaltered or slightly depressed; the cardiac output is increased about 50 per cent, and the ventilation is increased. It is suggested that these symptoms are due to stimulation of the chemoreceptors in the carotid sinus. Sometimes nausea begins thirty to sixty minutes later. Copious vomiting may occur.

These symptoms are generally accompanied with an intense feeling of discomfort to the patient, who has a pulsating headache, palpitations and subjective dyspnea.

In summary, the discomfort is so intense that, once experienced, it prevents an overwhelming majority of patients from further attempts to take alcohol as long as they are influenced by antabus.®

The clinical effect of alcohol after ingestion of antabus® is due to an increased concentration of acetaldehyde, which is formed by some unknown reaction of tetraethylthiuram disulfide on the enzymes oxidizing alcohol in the organism.

The initial dose is 2 Gm. the first day and 0.75 to 1 Gm. on the next two days. The subsequent dose depends on the individual subject and is adjusted so that flushing occurs after 5 Gm. of alcohol is ingested. This dose lies between 0.25 and 0.75 Gm. daily. The hypersensitivity to alcohol generally begins three to four hours after the ingestion of a single dose of antabus® and is fully developed during the next twenty-four hours.

No pathologic changes were observed as a result of use of the drug. Since September 1948 it has been used on several thousand patients in Denmark, Sweden, Iceland and Finland. Side effects were few—an occasional slight cutaneous allergic reaction, a manic state during the first weeks of treatment, in 2 or 3 patients and convulsions (probably due to intense hyperventilation) in a few patients.

It is inadvisable to treat patients as outpatients during a period of heavy drinking. They require hospitalization, and medication should not begin until all alcohol has disappeared from the body.

No absolute contraindications have been seen thus far. Caution is necessary in persons with heart failure.

Besides the medical treatment, which effectively stops the consumption of alcohol, the patients have been subjected to intensive psychotherapy, including group therapy, aimed at mental and social rehabilitation. Physical rebuilding was sustained with administration of vitamin B preparations and insulin in some cases.

In this treatment, relapses do not play the serious role they do in other treatments of alcoholism. Relapses are seen in patients who have discontinued medication or who are treated with too small doses.

Ninety-nine persons with alcoholism were treated with this substance and were observed six months or more. After six months of observation, 52 were regarded as socially recovered and 19 as much better. The medication must be combined with intensive psychotherapy in order that the results may be permanent.

ALPERS, Philadelphia.

A FOLLOW-UP REPORT OF SPINAL CORD INJURIES IN A GROUP OF WORLD WAR II PATIENTS. RICHARD C. SCHNEIDER, JOHN E. WEBSTER and JAMES E. LOFSTROM, J. Neurosurg. **2**:118 (March) 1949.

Ninety-four patients with penetrating wounds of the spine were observed and treated during the overseas period of their injuries; 69 of these were Americans. Follow-up reports made on 56 patients from two to three years after their injury form the basis of the present study. One patient had died; of the remaining 55 patients, 19 had had complete paraplegia. Four of these paraplegic patients had partially recovered, and 5 of them had been rehabilitated to a point of ambulation with braces. Twenty of the original 55 patients (36.3 per cent), 15 of whom were completely paraplegic, had shown no improvement. Sixteen (29 per cent) had no neurologic disability at the time of the report.

Forty-three per cent of the entire group were contributing to all or part of their support or were engaged in furthering their education. An almost equal number

were noncontributory. Eight of the patients with complete paraplegia were solely dependent on someone else for their support.

The methods of care, treatment and rehabilitation of patients with spinal cord injuries in use with the armed services deserve recognition and adoption by civilian medicine.

TOZER, Philadelphia.

RADIAL-MEDIAN ANASTOMOSIS. FRANK TURNBULL, J. Neurosurgery **5**:562 (Nov.) 1948.

The sensory loss resulting from injuries to the median nerve constitutes a greater handicap than the motor loss. Trick and supplementary movements minimize the loss of the intrinsic muscles of the hand innervated by the median nerve, but the loss of sensation over the index finger and the tip of the thumb is disabling.

The superficial radial nerve is entirely sensory, and its loss results in little or no disability. Anastomosis of the distal end of this nerve with the proximal cut end of the median nerve at the wrist is complicated by two factors: the discrepancy in size of the two nerves and the anastomotic technic.

In 3 of the 4 cases presented by the author the plasma technic of Tarlov was used. The onset of return of sensation varied from three months to one and a half years after the anastomosis had been performed. One of the 4 patients referred all sensation to dermatomes of the radial nerve for a period of eighteen months after operation. The other 3 patients "transposed" sensation to the area of the median nerve from the beginning of returning sensation.

TOZER, Philadelphia.

ELECTROSHOCK AND ELECTRONARCOSIS (ELECTROCOMA) IN TREATMENT OF MENTAL DISEASE. A. S. PATERSON, Acta neurol. et de psychiat. Belg. **48**:467 (Oct.) 1948.

Paterson compares the effects of electroshock and electronarcosis in treatment of mental disorders. The effects of electronarcosis in treatment of schizophrenia are different from those of electroshock; the hallucinations and illusions disappear more readily. Whereas similar changes may occur with intensive electroshock therapy, electronarcosis is much less dangerous. The author feels that electronarcosis constitutes a definite progress in psychiatric therapy, not only because it is less hazardous, but because it can be combined with other psychotherapy.

DEJONG, Ann Arbor, Mich.

SURGICAL TREATMENT OF SYMPTOMATIC FOCAL EPILEPSY. L. SCHWARZ, Acta neurol. et. psychiat. Belg. **48**:380 (Aug.) 1948.

The pathologic basis for the surgical treatment of epilepsy is not at present sufficiently well established to permit the postulation of satisfactory results in all cases. "Cryptogenic" epilepsy and disorders with onset in infancy respond less favorably than post-traumatic seizures in the adult. The time of onset of the disorder is an important factor in the prognosis. The coexistence of other disorders of the nervous system constitutes a serious contraindication to the surgical approach. A careful clinical examination and adequate localization are necessary before surgical treatment is considered.

DEJONG, Ann Arbor, Mich.

Muscular System

ISOLATED, PROGRESSIVE, SYMMETRICAL DYSTROPHY OF THE PECTORALIS MAJOR MUSCLES. HARRY TEITELBAUM and RUTH P. LEWIS, Dis. Nerv. System **9**:60 (Feb.) 1948.

Teitelbaum and Lewis recount the case of a white man aged 35 who came to medical attention because of probable idiopathic convulsive disease. Neurologic examination revealed partial symmetric atrophy of the upper digitations of the sternocostal portions of the pectoralis major muscles, without significant weakness of the remainder of the muscles. Electrical studies showed no reaction of degeneration, indicating the primary nature of the wasting. Creatine was found in the urine. The patient stated that he had noted progressive loss of bulk of the muscles of the chest for four years. He knew of no family history of a similar disorder. The authors believe that this is a sporadic case of muscular dystrophy, fitting into the category of Oppenheim's abortive type or Wilson's formes frustes. It is admitted that the process is still active and may ultimately spread to other muscles.

BEATON, Tucson, Ariz.

PATHOGENESIS OF MYASTHENIA. I. LESNY, Encéphale **38**:363, 1949.

Lesny reviews the literature and analyzes the various theories regarding the pathogenesis of myasthenia; namely, the neurovegetative, endocrine (thyroid, parathyroid, thymus, pituitary), infectious and toxic. He affirms the relation of the thymus to myasthenia, with the hypophysis acting indirectly by way of the thymus or the sympathetic nervous system. The possible toxic effect of certain substances, such as lipids, may also be involved as one of the causes. In any event, he believes that myasthenia results from the presence in the blood serum of an excess of some substance. The origin of this unknown substance and its presence in the blood result from disturbances of the vegetative nervous system or an anomaly of the endocrine glands. Using 2 guinea pigs previously tested for their ability to swim with a 10 Gm. weight attached to one leg, he injected serum from a myasthenic patient into 1 animal and noted ptosis of the eyelids, a more rapid onset of fatigue and shortening of swimming time. Into the other animal, he injected myasthenic serum and neostigmine and noted an increase in length of swimming time, with less fatigue than in the animal not receiving neostigmine. In another experiment, he used an ultrafiltrate of myasthenic serum and obtained the same increase in fatigability as with whole serum. Injection of normal laboratory serum and of serum from a medical student as controls did not produce the rapid fatigue noted with the myasthenic serum.

ZINKIN, New York

Diseases of the Bone

MANIFESTATIONS OF FIBROUS DYSPLASIA OF BONE. FRANK WINDHOLZ, Am. J. Roentgenol. **58**:51 (July) 1947.

Involvement of the skull in cases of fibrous dysplasia of bone is rare when the skeletal involvement is monostotic. With moderate skeletal involvement, lesions of the skull occur in about one-half the cases; with severe involvement, the skull always participates. Occasionally, the lesions in the skull are the only roentgenographic changes, and may constitute the earliest lesion.

With limited cranial involvement, small cystlike blisters are observed in the bony vault. In cases of the more advanced stage, localized deformities with areas of translucence and increased density within the deformed areas are observed. In advanced stages, extensive, dense bony islands and spicules are visible in the

expanded parts. There may be deformities of the entire vault, the base of the skull and the facial skeleton. The face and the base of the skull are most commonly the sites of heavy deposits of bone. The latter picture is typical of leontiasis ossium. Fibrous dysplasia is the most frequent, but not the only, cause of leontiasis. Second in frequency is Paget's disease (osteitis deformans) of the facial bones. The original Virchow type is extremely rare.

The basic tissue change is replacement of the diploe by connective tissue structures (roentgenologic translucencies), in which irregular, poorly or completely ossified, nonlamellated bone tissue may develop (roentgenographic densities). Careful analysis of the roentgenologic changes in the skull will permit differentiation from neurofibromatosis (Recklinghausen's disease) osteitis deformans (Paget's disease) and xanthomatosis.

TEPLICK, Philadelphia.

GENERALIZED XANTHOMATOSIS WITH PULMONARY, SKELETAL AND CEREBRAL MANIFESTATIONS. EULYSS R. TROXLER and DAVID NIETMETZ, Ann. Int. Med. **25**:960 (Dec.) 1946.

Typical Hand-Schüller-Christian disease, with its triad of symptoms, consisting of defects in membranous bones, exophthalmos and diabetes insipidus, is now considered the craniohypophysial manifestation of lipid granulomatosis. Eosinophilic or solitary granuloma of bone is one form of generalized xanthomatosis, and not a new disease entity. Wherever there is reticuloendothelium, there can be lipid granulomatosis. Thus, the clinical symptoms produced depend on the tissues involved and the degree of involvement.

Troxler and Niemetz report a case of generalized xanthomatosis in a man aged 35 who had pulmonary symptoms, and at one time severe pain accompanied with dyspnea. He had had polydipsia and polyuria for about ten years prior to his admission to the hospital. Roentgenograms revealed large cystic areas with well defined borders involving both iliac bones, the right ischium and pubic bone and the neck and trochanteric areas of both femurs. There was also an area of destruction involving the anterior portion of the body of the first lumbar vertebra. The lungs showed evidence of fibrosis.

Numerous blood chemistry determinations were made over the course of several years. The results were all within normal limits except for the glucose tolerance tests. The five hour oral glucose tolerance tests on three occasions gave the following results: 82.9, 99.5, 63.3, 68.5 and 73.5 mg.; 80, 133, 121, 46, 59 and 76 mg.; 84, 148, 125, 98 and 84 mg., per hundred cubic centimeters of whole blood. Specific gravity of the urine did not exceed 1.005, and the urinary output varied between 6 to 10 liters in twenty-four hours.

A biopsy specimen was taken from the right ilium; the cystic area was found to be filled with grayish yellow, fibrous tissue. The bone bordering the cyst was denser than the surrounding bone. Microscopic examination revealed a granulomatous process with cells of reticulum type present in both large and small groups. Many of the cells were foamy, with rather sharp borders. Large numbers of eosinophils were scattered throughout. Osmic acid stain revealed many fat droplets within the foam cells. Smears and cultures of the specimen removed for biopsy revealed no aerobic or anaerobic bacteria.

The diabetes insipidus was controlled by the use of posterior pituitary powder given in 2 grain (0.130 Gm.) doses three times a day by nasal insufflation.

The case reported illustrates some of the protean manifestations which may occur in generalized xanthomatosis. The definitive diagnosis was made by biopsy of a lesion of bone. There was extreme pulmonary involvement with fibrosis and

resulting bilateral pneumothorax. It was this condition which forced the patient to seek hospital care. After pleural aspirations the lungs remained expanded for a year and a half without further treatment. Because of advanced fibrosis within the lungs, roentgen therapy to these areas was deemed inadvisable.

Apparently hypophysial involvement produced diabetes insipidus, which was well controlled by the use of posterior pituitary powder.

Lesions in the bone were limited to the vertebrae, pelvis and upper portions of the femurs. The pelvic lesions did not change in size after roentgen therapy. A pathologic fracture occurred through the lesions in the right femur. This healed with conservative treatment and without unusual delay.

GUTTMAN, Wilkes-Barre, Pa.

Encephalography, Ventriculography and Roentgenography

THE MYELOGRAPHIC DIAGNOSIS OF EXTRA-MEDULLARY CERVICAL SPINAL CORD TUMORS. BERNARD S. EPSTEIN and LEO M. DAVIDOFF, Am. J. Roentgenol. **55**:413 (April) 1946.

An expanding lesion in the cervical portion of the spinal canal may produce bony changes in the roentgenogram, but these are usually of late appearance. Pantopaque® (ethyl iodophenylundecylate) myelography offers a safe method for early diagnosis. Usually 3 cc. of the oil is introduced into the lumbar subarachnoid space and allowed to flow slowly into the cervical area by elevating the foot of the table.

A constant defect in the oil column is necessary for the diagnosis of tumor; the oil column should be run up to the foramen magnum. It is often impossible to prevent some oil from entering the basal cisterns, but it can usually be recovered by reversing the position of the head. Two reactions were observed, presumably from oil droplets in the cisterns. In 1 patient sudden, intense vertigo occurred one week after myelographic examination, with normal findings. It disappeared gradually over a period of four days. The other reaction was an intense headache, which occurred five days after the taking of a myelogram, which was also normal. It gradually disappeared in two days.

Of the 5 reported cases, a defect in the oil column was found in each. Operation confirmed the myelographic findings. Three of the tumors were perineural fibroblastomas, and 2 were meningiomas. They were all removed completely, with full recovery.

TEPLICK, Philadelphia.

THE ROENTGENOGRAPHIC APPEARANCE OF THE FALX CEREBRI. E. GRAEME ROBERTSON, Am. J. Roentgenol. **56**:320 (Sept.) 1946.

By experimental and clinical study, Robertson showed that the falx absorbs more roentgen radiation than the surrounding brain tissues and therefore may be visualized on anteroposterior and posteroanterior roentgenograms of the skull if the rays are perfectly parallel with the plane of the falx. Slight deviations from this plane will so diffuse the shadow that it cannot be identified. Unusual density of the cranial bones or a pronounced diploic pattern will obscure the shadow of the falx.

A displaced falx indicates a mass lesion. Of 50 cases of proved neoplasm, the falx was seen in 28. In 15 cases it was central, and in 13 it was displaced away from the involved side.

TEPLICK, Philadelphia.

ROENTGENOLOGIC FINDINGS IN MYASTHENIA GRAVIS ASSOCIATED WITH THYMIC TUMOR. C. ALLEN GOOD, Am. J. Roentgenol. **57**:305 (March) 1947.

Good reviewed 100 consecutive cases of myasthenia gravis.

In each a posteroanterior roentgenogram of the chest and either a fluoroscopic examination or a lateral roentgenogram of the chest or both were made.

In 17 cases there was roentgenologic evidence of a mass in the anterior mediastinum. Of these, surgical exploration was made in 11 and postmortem examination in 3 others. In all 14 cases there was a tumor of the anterior mediastinum, in 13 of which it proved histologically to be of thymic origin. In the 1 case histologic changes were indeterminate.

Roentgenologically, two types of tumor may exist. The first type produces a well defined shadow, which will be disclosed by any type of roentgenographic examination of the thorax. The other type of tumor is shaped like a plaque and is closely attached to the anterior pericardium and great vessels. The only evidence of this tumor may be a shadow, best described as a "fulness" in the clear space of the anterior mediastinum. It may pulsate because of proximity to the heart.

Most of the tumors in the present series were in the upper mediastinum, overlying the aortic arch and the base of the heart. None was above the suprasternal notch. In 3 cases the tumor was lower, being at the level of the ninth thoracic vertebra.

Calcification of the tumor was found roentgenologically in 2 cases.

TEPLICK, Philadelphia.

PRIMARY HEMANGIOMA OF THE SKULL. B. D. WYKE, Am. J. Roentgenol. **61**:302 (March) 1949.

Wyke reviewed 40 cases of verified primary hemangiomas of the skull and found that these tumors constituted about 0.2 per cent of all osseous lesions and about 10 per cent of primary benign tumors of the skull. The average age for the patients was 29.8 years, though the lesions might occur at any age. While the tumor may develop in any bone of the skull, it seems to have a predilection for the parietal bone.

A history of local trauma often precedes the lesion. The tumor is usually palpable and visible; it is quite hard, is not tender and only rarely pulsates. No audible bruit is detected. There may be headache, but neurologic symptoms are unusual unless the tumor is in one of the smaller bones of the skull and produces pressure on adjacent structures.

The roentgenologic appearance is rather characteristic when the tumor is in the vault. In direct (anteroposterior) views there is a circumscribed oval, rarefied area, within which the tissue has a honeycombed appearance. No reactive sclerosis or increased vascularity around the lesion is seen. In profile views a radial striation produces a sun ray appearance. The external table of the skull is eroded and expanded, while the inner table is preserved. Pathologically, nearly all hemangiomas of the skull are of the benign, cavernous type.

Surgical incision is not difficult and is usually highly successful. Roentgen therapy can be employed when the lesion is in a relatively inaccessible area, such as the petrous pyramids or the orbital bones.

TEPLICK, Philadelphia.

PREMATURE CLOSURE OF CRANIAL SUTURES. D. R. SIMMONS and W. T. PEYTON, J. Pediat. **31**:528 (Nov.) 1947.

Simmons and Peyton operated on 5 patients with craniostenosis, 3 boys between the ages of 8 months and 3½ years and 2 women aged 28 and 29 years, respectively. Craniostenosis is an anomaly in which the sutures of the skull close prematurely,

causing compression of the intracranial contents. Microcephaly gives most difficulty in the differential diagnosis of craniostenosis. In the large majority of cases it should be possible to distinguish between these two conditions at an early age. Mental retardation, one of the earliest symptoms of craniostenosis, is the most important indication for surgical intervention, and one which has received little emphasis in the past. It is impossible to repair damage which has already occurred to the brain, but further damage may be prevented by early craniectomy. Blindness is one of the commonest symptoms, and surgical intervention should be performed at the first indication of failing vision. Occasionally surgical measures may be necessary for the relief of severe and persistent headaches which may be associated with the disease. Because the bones of the skull in infants are thin and flexible, linear craniectomy will allow for adequate expansion of the brain and will allow the head to assume a normal shape. After linear craniectomy the bone tends to form bridges across the artificial suture lines and to arrest expansion; this is probably one of the reasons for poor results following surgical intervention in these cases. Tantalum foil interposed between the edges of the bone should prevent this regeneration and should allow continued expansion of the skull without additional operations. This method was employed in 2 of the authors' patients aged less than 1 year. One year after operation psychometric testing revealed that 1 of these patients had an intelligence quotient of 100, and he seemed in every way a normal child.

J. A. M. A.

DISCREPANCIES IN MYELOGRAPHY: STATISTICAL SURVEY OF 200 OPERATIVE CASES UNDERGOING PANTOPAQUE MYELOGRAPHY. W. B. SCOVILLE, W. H. MORETZ and W. D. HANKINS, Surg., Gynec. & Obst. **86**:559 (May) 1948.

Scoville and his associates had gained the impression that myelography yields equivocal results in at least 25 per cent of cases. This is at variance with published statistics. They analyze 200 consecutive cases in which patients were subjected to myelographic study with pantopaque® (ethyl iodophenylundecylate) and operation for a ruptured lumbar intervertebral disk at the Cushing General Hospital. Four cases of lumbar spinal tumors were excluded from the statistics. Ruptured disks were found in 173 of the remaining 196 cases in which operation was performed. Findings in the 23 other cases were swollen nerve roots, adhesions, bony ridges, a fractured facet (1 case) and, more commonly, nothing. Double disks were found in 11 per cent. Over-all errors occurred in 65 of 196 cases. In order to rule out the personal equation from these diagnostic errors, the authors made a comparison with two surveys carried out by other investigators. Clinical evidence of a ruptured disk is more important than is myelographic evidence. A positive myelogram is more important than a negative one. A normal myelogram in the face of clinical evidence of a ruptured disk will be wrong three out of four times. Myelography fails to rule out the presence of a laterally placed lumbosacral disk. When myelography is used as the sole diagnostic criterion, the over-all error is in the neighborhood of 25 to 35 per cent, in contrast to the 6 to 8 per cent cited in the literature. The authors will continue to use myelography routinely in all cases in which ruptured disks are suspected, but will tend to discount all normal myelograms if the findings are contradicted by the clinical findings.

J. A. M. A.

Congenital Anomalies

CONGENITAL DEFECTS IN YEAR OF EPIDEMIC RUBELLA. R. E. OBER, R. J. M. HORTON and R. F. FEEMSTER, Am. J. Pub. Health **37**:1328 (Oct.) 1947.

Ober and his associates report a survey made in Massachusetts to detect anomalies in infants resulting from maternal rubella. The year 1943 was selected for such a study for several reasons: Nearly 35,000 cases of rubella had been

reported during that year, nearly twice the usual incidence; it was recent enough for individual memories to recall important facts; the children would be old enough for the anomalies to have been recognized. Of 54 pregnancies complicated by rubella reported on in replies to questionnaires sent to women of child-bearing age, 8 resulted in infants with abnormalities and 9 ended in abortions for stillbirths. Eleven of these 17 abnormal pregnancies were in women who contracted rubella during the first trimester. Of 9 pregnancies reported by the physician in response to questionnaires, only 3 produced normal infants. Eight of the 9 women contracted rubella in the first trimester. The authors admit, however, that caution is necessary in attributing all such defects in infants to maternal rubella. They stress the need of more comprehensive surveys to determine the comparative incidence of abnormal pregnancies associated with other virus and bacterial diseases, as well as abnormalities in pregnancies not complicated by communicable diseases.

J. A. M. A.

ROLE OF RUBELLA OR OTHER INFECTIONS OR TOXIC FACTORS OCCURRING IN COURSE OF GESTATION IN GENESIS OF CONGENITAL MALFORMATIONS AND DYSTROPHIES. G. LEFEBVRE and J. MERLEN, Ann. paediat. **171**:266 (Nov.-Dec.) 1948.

Lefebvre and Merlen reviewed the records of 2,247 pediatric cases with regard to pathologic conditions occurring during gestation. In 34 cases the mother had been ill during pregnancy; in the 14 cases in which the disorder had occurred after the third month of gestation, the fetus had not been influenced by it. In the 20 cases in which the maternal illness had occurred during the early part of the pregnancy, the following defects were detected in the offspring: cataracts, 4 cases; defects of the heart, 6 cases; backwardness with microcephaly, 6 cases; mongolism, 2 cases; cleft palate, 1 case, and syndactyly, 1 case. The disorders observed in the mothers of these defective infants were as follows: rubella (fetal cataract resulted), 1 case; influenza, 4 cases; therapeutic shock in the course of infection, 3 cases; septicemia, 2 cases; scarlet fever, 1 case, and mumps, 1 case. The authors do not feel justified in drawing definite conclusions but believe that, besides rubella, numerous infections or toxic factors that occur during early pregnancy may exert an adverse effect on the product of conception.

J. A. M. A.

Society Transactions

NEW YORK NEUROLOGICAL SOCIETY

Samuel Brock, M.D., President, Presiding

Regular Meeting, Feb. 3, 1948

Pia-Arachnoid Cysts of the Posterior Fossa: Report of Two Cases. DR. ABRAHAM KAPLAN.

The occurrence of pia-arachnoid cysts in the midline of the posterior fossa is rare, and a thorough search of the literature has revealed only 3 cases. To these cases 2 others are added.

CASE 1.—M. R., a man aged 32, was admitted to the Mount Sinai Hospital on Jan. 18, 1937 because of headaches, vomiting and failing vision. For five or six years before admission he had experienced morning vomiting, which at times was projectile and associated with suboccipital headache. He had been treated for various "stomach ailments" by different specialists, but repeated roentgenologic studies revealed nothing abnormal.

Five months before admission he suddenly experienced diplopia, which recurred at weekly intervals. He noted that he was unsteady in gait, with a tendency to stagger to either side. Subsequently he noted difficulty in swallowing and some diminution in libido. When papilledema was discovered, he was promptly admitted to the hospital.

Examination showed the following abnormalities: (1) slight bilateral exophthalmos; (2) a broad-based gait, with veering to the left; (3) a positive Romberg sign; (4) bilateral papilledema of 3 D. and enlargement of the blindspots; (5) horizontal nystagmus with ataxia in the finger to nose test; (6) a bilateral Babinski sign; (7) absence of abdominal reflexes, and (8) a spinal fluid pressure of 200 mm. The fluid was otherwise normal.

A suboccipital craniotomy, performed on January 25, disclosed a translucent cyst, measuring 3 by 4 cm., which contained clear fluid and was situated in the midline. This cyst was independent of the fourth ventricle; the vermis was flattened, and the cerebellar hemispheres were markedly displaced from the midline. The arachnoid cyst was removed, and the postoperative course was smooth and uneventful. Pathologic study of the wall of the cyst showed no neoplastic elements but revealed flat cells simulating the arachnoid membrane.

The patient has been in excellent health for over ten years and has carried on his daily occupation.

CASE 2.—R. A., a married woman aged 37, was first seen on July 10, 1946 because of impaired vision in the left eye. Five months before admission she began to have headaches in the right parietal area with blurring of vision in the left eye. Two months later there were nausea and vomiting almost every morning. For two months before admission, on awakening, she experienced stiffness in the back of the neck, with a tendency to unsteadiness of gait.

Examination showed that the left pupil was larger than the right and revealed acute bilateral papilledema with flame-shaped hemorrhages. Vision was 15/100 in the left eye and 15/20 in the right eye, and the blindspots were enlarged. The

rest of the neurologic examination was noncontributory. The results of laboratory studies were within normal limits. A roentgenogram of the skull showed atrophic changes in the dorsum and the clinoid processes of the sella turcica. The patient was obese. Electroencephalograms gave evidence of a diffuse disturbance. Ventriculographic examination showed symmetric dilatation of both lateral ventricles and dilatation of the third ventricle up to the aqueduct of Sylvius.

Suboccipital craniotomy, performed on July 15, revealed a bluish cyst, measuring 3.5 by 4 cm., in the midline. The cyst contained clear fluid and was separated from the roof of the fourth ventricle. The vermis was compressed anteriorly, and both cerebellar tonsils were somewhat herniated through the foramen magnum. Both cerebellar hemispheres were displaced laterally from the midline. After removal of the cyst, the postoperative course was unusually smooth. The papilledema subsided completely, and vision in the left eye improved from 15/100 to 15/70. Pathologic study of the wall of the cyst showed hyalinized connective tissue and a few blood vessels. There was no evidence of any neoplastic elements. The patient has remained well since the operation; she stated that she had not felt so well in five years.

Comment.—Pia-arachnoid cysts of the posterior fossa in adults must be differentiated from those found in infants and children. Cysts of the former type present the typical picture of a progressively expanding lesion of the posterior fossa, with a history of recurrent headache, vomiting and instability in gait extending over a period of years, with intervals of freedom, a course somewhat unusual for a neoplasm. It is believed that these arachnoid cysts are not congenital but developmental and that they form as a result of blocking of one or several of the perforations in the roof of the fourth ventricle.

DISCUSSION

DR. IRA COHEN: It is from the operative description of these interesting cases presented by Dr. Kaplan that one can distinguish this cyst from other collections of cystic fluid in the posterior fossa. In the large group of the adhesive collections of fluid in the arachnoid, described by Horrax (Generalized Cisternal Arachnoiditis Simulating Cerebellar Tumor, *Arch. Surg.* **9**:95 [July] 1924), the fluid is found in the cisterna magna, the walls of which are thickened and opalescent. In the series of cases collected by Taggert and Walker (Congenital Atresia of the Foramens of Luschka and Magendie, ARCH. NEUROL. & PSYCHIAT. **48**:483 [Oct.] 1942) the cystic fluid was found in the fourth ventricle. The thinned roof of the fourth ventricle formed the outer boundary of the cyst. In many such cases the cyst is associated with agenesis or partial agenesis of the cerebellum. One such case was presented before this society several years ago—that of a boy aged 13 years in whom operation revealed a huge cyst with agenesis of the cerebellum, and who had the internal hydrocephalus shown on the lantern slide. It is also evident that the posterior fossa was much larger than it should have been. This condition does not necessarily occur only in children; this patient was 13 years old, and cases have been described both in adults and in adolescents. The fluid in the cases described by Dr. Kaplan was outside the cavity of the fourth ventricle, and outside the cavity of the cisterna magna; in that way one distinguishes this cyst from other collections of cystic fluid. I am not prepared to give any explanation of the mechanism of formation of these cysts. From the location of the fluid, I do not see how it could have anything to do with the closure or the absence of opening of the foramens of Luschka and Magendie. I rather think that it is an arachnoid cyst, such as might occasionally be encountered in various places

in the central nervous system. I recall having had a case of such a cyst in the subarachnoid space of the spinal canal in the thoracic region. I have had 2 cases of the cyst above the tentorium. Two other cases of the cyst in the posterior fossa resemble those presented by Dr. Kaplan this evening. One was the case of an 8 year old boy who presented a similar picture and who remained well for the five years during which he reported for follow-up study. He has not been around for two years. The other case was presented by Dr. B. C. Meyer several years ago. The cyst was associated with anatomic platybasia. The patient showed much improvement after operation, having had partial paralysis before it. She returned to the hospital about a year later and died without operation; autopsy revealed a glioma of the pons—not that I believe this tumor had anything to do with the cyst formation. Many of these cysts contain yellowish fluid. However, most of them contain clear fluid, as Dr. Kaplan has described. I believe this cyst represents a type which is distinct from the congenital malformation and dilatation of the fourth ventricle due to failure of the foramens of Magendie and Luschka to open, as well as from the ordinary arachnoidal inflammatory or traumatic collection of fluid.

A System of Diagnostic Electroencephalography. DR. HANS STRAUSS.

The diagnostic use of electroencephalography is based on a great deal more than an analysis of the electroencephalogram. On the basis of the electroencephalogram alone a statement can be made which either simply describes the record or, if a classification has been made before, classifies it as a certain type of electroencephalogram. The electroencephalographer may go one step further and interpret the record in general physiologic terms, stating that it indicates a diffuse or focal disorder, and paroxysmal or nonparoxysmal, or some other type, of dysfunction. However, even such statements are often of little value to the clinician, who confronts the electroencephalographer with requests to express an opinion on the specific diagnostic significance of a certain type of electroencephalogram. A valid basis for such an opinion can be obtained by classifying the records and attempting to correlate certain types of records with specific clinical conditions. Only after such correlations have been established can one even begin to use the electroencephalogram as an aid in diagnosis.

Classifications of records have been described before, the most important ones being those of Gibbs, Gibbs and Lennox (Electroencephalographic Classification of Epileptic Patients and Control Subjects, ARCH. NEUROL. & PSYCHIAT. **50**:111 [Aug.] 1943) and Jasper and Kershman (Electroencephalographic Classification of the Epilepsies, ARCH. NEUROL. & PSYCHIAT. **45**:903 [June] 1941). Both systems deal primarily with convulsive disorders and do not consider in detail those types of records obtained from patients with organic diseases of the brain. My colleagues and I felt the need, therefore, of a more comprehensive system of diagnostic electroencephalography.

First, one has to consider whether a record is normal or abnormal. Evidently this will depend on what one calls normal or abnormal clinically. We consider as abnormal subjects with a disturbance of cerebral function, associated with histologic cerebral changes, subjects with paroxysmal cerebral disorders of unknown origin, subjects with disturbance of cerebral metabolism and subjects with psychiatric disorders. In contradistinction, we consider as normal subjects without evidence of any such disorders, and we classify as normal records which as a rule, and not with rare exceptions, are obtained from such subjects. With the standards so obtained, we consider as normal many records classified as abnormal by a number

of investigators. We refer in particular to such records as those classified by Gibbs, Gibbs and Lennox (previously cited) as S_1, F_1 and F_2. The correlation between electroencephalographic and clinical abnormalities would become almost perfect if these workers would consider these records as normal, as we propose to do. Then, too, the results of other authors, who obtained abnormal records from 30 per cent of their normal controls (Finley, K. H., and Campbell, C. M.: Electroencephalography in Schizophrenia, *Am. J. Psychiat.* **98**:374-381, 1941), would lose their seeming significance, and the confusing group of so-called borderline records would become an extremely small one. The matter of normal records is of crucial importance because in many instances the statement that a record is abnormal will in itself have great practical significance, as, for example, in cases in which the question of post-traumatic cerebral damage has to be decided.

In discussing types of abnormal records, we limit ourselves to the electroencephalograms of adults. The following types of abnormal records are described:

A. Abnormal distribution of alpha activity
   1. Unilateral depression
   2. Occipital depression
   3. Extinction in one or more leads
B. Bursts
   1. Delta waves — (a) Diffuse
   2. Spike and dome pattern — (b) Symmetric
   3. Spikes and sharp waves — (c) Shifting
   4. Hypersynchrony — (d) Focal
C. Abnormal sleep
D. Irregular delta activity

Type A 1 was discussed several years ago (Strauss, H.; Liberson, W. T., and Meltzer, T.: *J. Mt. Sinai Hosp.* **9**:957-962, 1943). This type of record indicates a loss of functioning cerebral tissue, such as is seen in cerebrovascular disease and multiple sclerosis and as a transitory phenomenon in unilateral cerebral anemia, such as follows ligation of the common carotid artery. Type A 2 is seen with a traumatic lesion of both occipital lobes. Type A 3, described first by Jasper and associates (Electroencephalographic Studies of Injury to the Head, ARCH. NEUROL. & PSYCHIAT. **44**:328 [Aug.] 1940), is found most frequently when a short-circuiting mass is interposed between the electrodes and the cerebral cortex, as in subdural hematoma and above thallium plates.

The types in groups B and C are not discussed in detail. Within group D we distinguish twelve types of records, according to (*a*) the high or low degree of abnormality; (*b*) asymmetry, symmetry or parasymmetry and (*c*) focal or diffuse abnormality. The characteristics for the degree of abnormality and the degree of asymmetry are as follows:

High abnormality
   Lowest frequency 2 or less cycles per second
   Average delta factor 20 or more
   Delta factor at least 35 in one lead
Low abnormality
   Any one of these conditions not fulfilled
Asymmetric abnormality
   Delta quotient more than 1.5 in records of high abnormality and more than 2 in records of low abnormality
Parasymmetric abnormality
   Delta quotient lower, but record not symmetric

A delta wave is defined as a wave with a frequency of 6 or less cycles per second and a voltage of at least 20 microvolts. The delta factor indicates the percentage of the total length of record occupied by delta activity. The delta quotient is the number obtained by dividing the sum of the delta factors from the side of the brain with the greater amount of delta activity by the corresponding number from the other side. The method uses numerical criteria, which are

necessary if one wishes to arrive at anything approaching objective standards. The values were obtained after repeated attempts to classify the records in a way which would make the classification useful for diagnostic purposes. The distribution of delta activity in a given electroencephalogram can be demonstrated at a glance if the delta factors in the various leads are plotted in the form of a graph (Strauss, H.: Electroencephalographic Studies: Diagnosis of Abnormal Electroencephalograms, *J. Mt. Sinai Hosp.* **9**:17-22, 1942).

In correlating clinical diagnoses and types of records, one must be aware of the fact that a correlation between any electroencephalogram and a disease entity is influenced by the stage of development of the disease at the time the electroencephalogram is taken. We have tables showing the frequency with which all the various types of records occur with all the diseases seen, and I present two tables, one on cerebrovascular disease and the other on supratentorial tumors, respectively.

Tables like these are of no immediate value in diagnostic electroencephalography. For diagnostic purposes one needs tables showing the various conditions which are found associated with a certain type of record and the percentage of patients with a certain disease showing this type of record. Some of these types of records, e. g., those with asymmetric and focal abnormality, occur only with a relatively small number of conditions and with varying frequency in different conditions. Other types of records, e. g., those with symmetric and diffuse delta activity, occur in a great variety of clinical conditions associated with diffuse, nonparoxysmal cerebral dysfunction, such as diffuse cerebral disease, tumors of the posterior fossa with internal hydrocephalus, disturbance of the function of diencephalic centers and metabolic and circulatory disorders. While, therefore, the appearance of such a record cannot be used to differentiate the various causes of diffuse, nonparoxysmal cerebral dysfunction, it still has diagnostic significance by showing (1) that there is cerebral dysfunction and (2) that a focal lesion, in particular a tumor of the cerebral hemispheres, is improbable.

Tables such as those devised for all the types of records can be used in the differential diagnosis of various diseases, if they are consulted as to the relative frequency of occurrence of a certain type of record with these diseases. A table showing the relative frequency of occurrence of various types of records with cerebrovascular disease and with supratentorial tumors demonstrates that records without delta activity are six times, and records with a low degree of abnormality, symmetry and diffuse abnormality four times, as frequent with cerebrovascular disease as with tumor. On the other hand, records with a high degree of abnormality and asymmetry and a focus are thirty-two times, and records with a low degree of abnormality, parasymmetry and a focus, five times as frequent with tumors as with cerebrovascular disease.

On comparison of supratentorial meningiomas and other supratentorial tumors (gliogenous and metastatic), it becomes evident that records with a high degree of abnormality are much more frequent with nonmeningiomatous tumors. When one considers some of the clinical findings together with the electroencephalographic, the value of the latter is greatly enhanced: In more than one-half the cases of meningioma with jacksonian seizures the records were normal, and in no case of meningioma at the convexity with jacksonian seizures was the record abnormal. Therefore an abnormal record in a case with jacksonian seizures contraindicates the diagnosis of meningioma over the cerebral convexity.

The electroencephalogram can be of assistance in the diagnosis and differential diagnosis of tumors of the posterior fossa. An asymmetric record with a focus was never found in cases of cerebellar tumors, an observation which seems important

in differentiating them from tumors of the frontal lobe. All our patients with meningioma of the cerebellopontile angle showed normal records, while this was not true for all patients with acoustic nerve tumors. Therefore an abnormal record for a patient presenting the clinical syndrome of a tumor of the cerebellopontile angle is suggestive of an acoustic neuroma, as opposed to a meningioma.

Other problems in differential diagnosis, such as the differential diagnosis of multiple sclerosis and encephalitis, and that of various inflammatory cerebral diseases (abscess, encephalitis and meningoencephalitis) are discussed.

Many more valuable results can be expected after more data on the diagnostic significance of certain types of electroencephalograms in the presence of certain clinical signs have been collected. The system described is not considered final, but the hope is expressed that better systems will be developed.

DISCUSSION

DR. MARGARET RHEINBERGER (by invitation): I should like to express first my hearty agreement with Dr. Strauss's general discussion of the electroencephalogram and what it does. It seems to me that the electroencephalogram becomes of greatest value to the clinician who deals with changes in body function in which the brain is, or may be, involved when he considers the electrical technic as a means of demonstrating some of the disturbances which may have occurred in the physiologic and anatomic mechanisms of the functioning, three dimensional, brain.

I wish also to congratulate Dr. Strauss on his measurements and tables of correlation; they have taken him many hours to compile. Having measured miles of records myself, my automatic impression of any system of analysis which depends on measurement is that it will be of little use to the practical electroencephalographer because there will never be enough time to spend in measuring the details of the records to any fine degree. However, it will be noticed in Dr. Strauss's tables that the differentiations were on the basis of rather gross figures; i. e., asymmetric records were classified as those with twice, or one and a half times, as much of the delta disturbance from one side as from the other, whereas at least one third of the activity from a single area must be delta if the record is to be considered highly abnormal. Such large differences are easily visible, and much finer differentiations can be made by the trained eye, so that the application of a system such as Dr. Strauss's would not be very difficult. However, for general application in correlation with clinical material, I should prefer to have a system which included not only the delta activity, but also the changes which Dr. Strauss has described as occurring in the alpha category (to which I should add several others, such as an alpha potential which is 1, 2 or 3 cycles slower than that from the other side, even if it does not fall within the delta range, and the depressed alpha activity, which may also be abnormal). It is far in the future, however, before there will be any system which has been as adequately defined and worked out as Dr. Strauss's system for the clinical material involved.

With the consideration of the electroencephalogram as a representation of the physiologic changes which are occurring in the brain cells in response to abnormal changes, initiated either intracranially or extracranially, the application of the technic to the clinical field seems to me to be very much clarified. It is not, for instance, surprising that a space-occupying lesion with associated vascular disturbances, and surrounding edematous brain tissue, should give a tremendous amount of electrical change, or that such a situation should usually produce a high abnormality record in Dr. Strauss's classification. It is also not surprising that, in the large majority of instances, a meningioma lying over the convexity,

even though it may give jacksonian seizures, has affected such a very small area of the brain that the electric technic records the superimposed normal activity of the surrounding tissue in preference to that of the disturbed area. I have in my collection at least one meningioma lying over the convexity which did produce localized abnormalities electrically, but that does not invalidate in the least the generalization that in such a situation one would not expect to have any large amount of electrical disturbance.

It is this kind of correlation which Dr. Strauss's system helps to elucidate, and which I feel is a necessary approach to the utilization of electroencephalography in the clinical field.

DR. MARGARET A. KENNARD (by invitation): I have nothing to add to what Dr. Rheinberger has said. I would agree with her in every way. There are several diagnostic criteria in electroencephalography which, as I saw it, had not been fitted into Dr. Strauss's scheme, and I should like to have Dr. Strauss add these to his system; then one can use his figures.

DR. HANS STRAUSS: I wish to thank Dr. Rheinberger for her discussion. Whenever I listen to her, I learn something. Evidently, there are types of abnormal records, as she has just described, which escaped us because we did not pay attention to these features of the electroencephalogram. We shall do this in the future and incorporate into our system everything that proves to be of diagnostic value.

While we measured all the records when we originally devised our system of classification for the records with irregular delta activity, we do not measure most of the records now. Most of them can be classified without measurements, but the measuring becomes most valuable when there is doubt about the correct classification of a record.

Factors Affecting the Electroencephalograms of Children and Adolescents. DR. MARGARET A. KENNARD (by invitation).

The electroencephalograms of children with disorders of behavior are frequently abnormal, in spite of absence of demonstrable organic involvement of the nervous system. In a previous publication we have attempted to show that in children between the ages of 5 and 12 years there is about 70 per cent abnormality in the electroencephalogram, as shown by patients admitted to the psychiatric ward of Bellevue Hospital. This abnormality could not be shown to relate to epileptic symptoms or to epilepsy in the family. The incidence of abnormal electroencephalographic patterns was, however, related to the duration and early onset of clinical disorder and to the presence of neurotic or psychotic symptoms in other members of the family.

In the present study, the electroencephalograms of 529 patients between the ages of 6 and 24 years have been evaluated. No patient had signs of organic involvement of the nervous system. All were patients in the psychiatric wards at the time of the electroencephalographic examination.

The incidence of abnormal electroencephalograms is related to age. In the 6 to 7 year age group, 81 per cent of records were abnormal; in the 8 and 13 year group, 66 per cent were abnormal; in the 14 to 15 year group the percentage was 54, whereas above that, in the 16 to 24 year group, the incidence remained at 46 per cent. This agrees with the fact, previously shown by others, that the incidence of abnormal electroencephalograms is not so high in young adults with behavior problems as it is in children.

Another contributing factor is probably that of tension or anxiety. Previous evidence shows that this is related to temporary distortion of the electroencephalo-

gram, and in these children it probably correlates with abnormality of record. This is obvious when two groups of patients are compared: one, the schizophrenic patients who have marked anxiety; the other, the psychopathic patients who show little or no guilt or anxiety as the result of their behavior. Of 176 schizophrenic children, 68 per cent had abnormal electroencephalograms, while of 23 psychopathic children 32 per cent were abnormal—about half the number of schizophrenic patients.

The familial patterns found in electroencephalograms also contribute to the individual patterning. In a series of 73 patients and 135 of their normal siblings, all without signs of abnormality of the nervous system, striking similarities of pattern were found in members of a single family. When these persons were grouped in relation to normality or abnormality of their records, the following results were obtained: For 25 patients with normal records only 20 per cent of the relatives had abnormal records. For the 13 patients with borderline records, 26 per cent of the members of their families had abnormal records, whereas 40 per cent of the records of relatives of the 35 patients with abnormal records were likewise abnormal. This shows a familial incidence of normal and abnormal potentials which is clearly demonstrated on inspection of individual family records.

Finally, reexamination of records over a period of years for a series of 81 patients without organic involvement of the nervous system indicated some organization or improvement of electroencephalographic patterning with age. This tendency to a better patterning was definitely increased as a result of shock therapy. Records which were well organized and normal on first examination showed little change with time, but abnormal records, particularly those with paroxysmal activity, showed better organization with growth and development in 35 per cent of cases. After shock the incidence of improvement of the electroencephalogram was 50 per cent.

It would seem that the electroencephalogram is an objective record of organic changes within the cerebrum which are physiologically and chemically ordered. As such, it cannot be expected either to aid in the clinical diagnosis or to correlate with the complex psychologic traits of neuroses, psychoses or normal personality structure. But, as a psychologic instrument, it should be useful as an aid in the understanding of psychiatric processes, particularly in children, for various reasons:

1. The presence of an abnormal electroencephalogram in a child who has no traits suggesting epilepsy or other disorder of the nervous system should be suggestive of an early and deep-seated disorder of behavior.

2. The distorted record may be the result in part of tension or anxiety, a personality which is unusually responsive to environmental stimuli.

3. Part, at least, of the hyperreactivity of the cerebrum is due to heredity and familial patterning, such as has been found in the families of epileptic patients.

4. After shock therapy, the electroencephalograms of a significant percentage of children show an increase in stability and in uniformity of pattern. They are less reactive to hyperventilation.

5. These data suggest at least that fear, tension and anxiety affect the organism less after shock therapy, and the electroencephalogram is a sensitive indicator of this modification.

DISCUSSION

DR. LAURETTA BENDER: I have been deeply appreciative of the work that Dr. Kennard has done in electroencephalography on the children with whom I have been working for the past five years. Until she began to work with the children's

electroencephalograms, I was inclined to be resistant to what was more or less the accepted attitude toward dysrhythmias in children with behavior problems, to the concept of a poor prognosis and an organically determined disorder of behavior which is not readily corrected. I had felt that even the recognized organic disorders of the brain of children could be associated with a functional problem and with a much better prognosis than is generally accepted. I was loath to accept the electroencephalogram as evidence of an organic disorder in those children who did not have any other evidence of organic change; so I like very much the idea that the electroencephalogram is an expression of a physiologic, rather than a pathologic or structural, disorder in cortical function. Dr. Kennard's work has been very important from various points of view in what we have learned about children at Bellevue Hospital. In nonschizophrenic children and children with other nonorganic conditions, I have not looked on any one factor as responsible for the behavior problems. As factors which go into the making of the behavior problems of children who come to Bellevue, I have considered a broken home during infancy, belonging to a cultural minority or an inadequate intelligence quotient; in many instances there is an organic factor in addition. There are usually at least three, and in many instances all four, factors. I think one can say that one may include the factor of dysrhythmia in the electroencephalogram as contributory to the chances of a child's presenting a behavior problem.

There are two possible ways of accounting for the dysrhythmias: (1) There is a familial disorder of the pattern, or (2) there is an actual developmental difficulty of maturation in deeper physiologic patterns, as shown by the electroencephalogram. As to which is cause and which is effect, that is not yet determined. It does seem to be true in the case of children with nonorganic and nonschizophrenic disorders that the dysrhythmia in the record goes with a long period of what Dr. Kennard has called tension or anxiety. Whether these are the children who have electroencephalographic dysrhythmias, and the behavior disorder is the result of the inadequate cerebral patterning, or whether long periods of maladjustment lead to tension and anxiety, with the production of cerebral patterns, is not certain. But the evidence is fairly clear that these difficulties in maturation tend to occur first, and this conclusion is in keeping with clinical experience that the child's behavior problems tend to occur first. I should say now that educational difficulties, sociologic, ideologic and cultural problems and discrepancies in maturation of the cortical pattern, which are interpreted as dysrhythmias in the electroencephalogram, are independent of other, organic factors. The problem of the schizophrenic child is one which concerns me especially. The concept that the greater incidence of dysrhythmias which is found in schizophrenic children is related to what I call an excessive plasticity of the organism that suffers from schizophrenia in early childhood is an enlightening one. Certain it is that the schizophrenic children whom I have observed, in considerable numbers, show a remarkable plasticity of the total organism in integrating cerebral function, and correlated with this plasticity there is a tendency for the schizophrenic child to show an exaggeration of all kinds of disorders, whether they be vasomotor disorders, disorders in vegetative functioning or disorders in relationships to other people.

It has been extremely interesting that Dr. Kennard's work has shown that after shock treatment this plasticity is reduced, for this observation is in keeping with our clinical experience, namely, that the child after shock treatment shows improved relationships and what we consider clinically as a more normal pattern of behavior, and is able to get along better with his schizophrenia. That is a long way from saying that the dysrhythmia is related to the schizophrenia in a causative way, rather, the organism as a whole functions in dysrhythmic patterns,

which appear to be made more compact with shock treatment. This work is in line with our aim in all our therapeutic attacks, namely, the normal maturation pattern. Especially in children do we try to make the organism conform to the normal maturation drive, rather than to deviate from it, which is the tendency of the schizophrenic person. I am appreciative of Dr. Kennard's work in throwing more light on what we have been trying to accomplish in studying the behavior problems of children from various points of view.

DR. MORTIMER OSTOW (by invitation): I had the privilege of working in one of the institutions in which work similar to that reported by Dr. Kennard was first done, that is, the Medical Center for Federal Prisoners in Springfield, Mo., where I followed Dr. Daniel Silverman, one of the early reporters on this work (Clinical and Electroencephalographic Studies on Criminal Psychopaths, ARCH. NEUROL. & PSYCHIAT. **50**:18 [July] 1943). Silverman and Rosanoff (*J. Nerv. & Ment. Dis.* **101**:311 1945) reported on homosexual and criminal psychopathic persons, and I wish that my colleagues and I had had some of the opportunities which Dr. Kennard has had of following up our work. Silverman also administered shock therapy to psychopathic persons whose ages ranged from 17 to 23. They were studied by repeated electroencephalographic recordings, as well as by clinical observation. Over a period of about six months no significant permanent alteration was found in the psychiatric pattern, none in the psychometric pattern and none in the electroencephalogram. There was one other difference in our population; Dr. Kennard has mentioned that abnormalities were found among both the children with behavior disorders and, perhaps even more definitely, the schizophrenic children. At our institution, where the youngest patients were between 15 and 16, we could distinguish quite clearly between the psychopathic personalities, on the one hand, and the psychotic patients, on the other. The psychotic patients almost invariably had normal electroencephalograms, whereas the psychopathic patients frequently had abnormal records. We made fairly full studies of the personality patterns and the electroencephalograms, and we failed, although we studied about 2,000 patients, to find any definite relation between any particular personality trait or any history of a particular personality deviation in the patient's childhood and a specific electroencephalographic abnormality. By this, I mean we could not take any one trait, enuresis for instance, and say it was more frequently associated with an abnormal than with a normal electroencephalogram. Finally, in our experience with patients with psychiatric disorders, aside from those who demonstrated high voltage paroxysmal bursts, the abnormalities were of a much smaller degree of magnitude than the abnormalities described by Dr. Strauss and Dr. Rheinberger as occurring in patients with brain tumor and head injury. The disparity between Dr. Kennard's findings in patients under 12 years of age and ours in patients over 16 years of age poses a formidable problem, to which we shall have to address ourselves in the near future.

DR. BERNARD PACELLA: A particular aspect of Dr. Kennard's discussion has interested me; this relates to the observations on the schizophrenic children who received shock therapy and the significance of those observations. During the past several years, at the Psychiatric Institute, my colleagues and I have studied a fair number of schizophrenic children, and we have not been able to find any relation between the degree of clinical deterioration and the degree of electroencephalographic abnormality. As a matter of fact, we have not been impressed by any unusual amount of abnormality in the group, as compared with that associated with the primary types of behavior disorders, such as the neurotic disturbances and the conduct disorders. In patients who had received shock therapy

—and I speak more particularly of the adult patients, since we have not given our schizophrenic children much shock therapy—the electroencephalogram did show a tendency to an apparently "more normal" pattern, after the immediate post-treatment abnormality; this "more normal" pattern manifests a higher incidence and a higher amplitude of alpha waves. Many of the patients whose records initially showed predominantly low voltage fast activity and practically no alpha activity frequently exhibited this pronounced alpha rhythm after treatment. In experimental animals, particularly the monkey, to which we have administered long courses of electric convulsion treatments, similar to the therapy we gave human subjects, we have noted a similar increase in the appearance of alpha waves after the initial appearance of slow potentials. I do not believe that a strong alpha rhythm can necessarily be interpreted as a more normal record; furthermore, what appears to be a more normal record does not necessarily imply a more normal mental status. It is more likely to be related to a physiologic change which tends to facilitate the so-called alpha rhythm.

DR. MARGARET KENNARD: I am aware of Dr. Ostow's work with Dr. Silverman. It is interesting that, but not yet clear to me why, the statistics for criminals always seem to differ from those obtained from the psychiatric hospitals. I have discussed this with Dr. Simons, who has been working in Dr. Diethelm's department, and I believe it is because the definition of the psychopathic personality is not the same in all clinics. I must therefore disagree with the point that Dr. Ostow makes about the psychopathic patients having more abnormal records than schizophrenic patients, and I believe I am backed by the data of other investigators. The best source is Greenblatt's figures, which showed 40 per cent of abnormal records for all the major groups of psychoses and a very high percentage for the neuroses. I did not mean to say that the children with schizophrenia had a higher percentage of abnormal records than the children with behavior disorders. Actually, in the whole series the percentage of abnormal records for schizophrenic children was 72, and that for the behavior disorders was 67; so there is no true difference in the incidence of abnormal records for the two groups.

My figures agree well with Dr. Pacella's. We made electroencephalograms on a large series of adult patients before, during and after shock therapy, and we found, as Dr. Pacella has in children, that the records which are most stable and have the most alpha activity are those which are least affected by electric shock therapy after the first shock, after the third, and so forth, and are those which return to normal most quickly. The records which are strikingly dysrhythmic preceding shock therapy are immediately distorted by shock therapy and sometimes show an increase in their dysrhythmia after the period of recovery from shock. That is in keeping with a previous report of Dr. Pacella on several patients who had clinical epilepsy after shock but had not had it previously.

I did not mean to say that the reorganization of the electroencephalogram after shock had any correlation with the amount of clinical recovery; in fact, I intended to say it had not. We found no correlation between clinical changes and the reorganization of the electroencephalogram after shock.

If I could leave you with the idea that the electroencephalogram of children is more sensitive to all kinds of stimuli than that of adults, a fact which is well known, and that from inherited and various other factors the patterning of children with behavior disorders is more rapidly influenced by these various stimuli, I have accomplished what I meant to do in this résumé. In the end, this problem will come down to a discussion of conditioned processes and the ease or relative difficulty with which the maturing cerebral cortex becomes conditioned from environmental and other types of stimuli.

NEW YORK NEUROLOGICAL SOCIETY AND THE NEW YORK ACADEMY OF MEDICINE, SECTION OF NEUROLOGY AND PSYCHIATRY

Samuel Brock, M.D., *President, New York Neurological Society, Presiding*

Joint Meeting, May 11, 1948

Cerebral Activity and Motor Functions: Role of Corticospinal and Subcorticospinal Mechanisms, with a Concept of the Origin of Abnormal Involuntary Movements. DR. ABRAHAM M. RABINER.

In the patient with spastic hemiplegia, the clinician expects to elicit the Babinski sign and to find the abdominal reflexes absent and the tendon reflexes hyperactive. He is not surprised if tone is diminished, rather than increased, and realizes that this is especially so when the postrolandic area is the seat of pathologic change, with resulting sensory impairment. He is aware also that a lesion of area 4 may result in increased reflexes and absence of spasticity. He is not, however, as easily reconciled when he cannot elicit the Babinski sign in the spastic lower extremity of the hemiplegic subject, or when a patient with amyotrophic lateral sclerosis presents hyperreflexia in all four extremities, spasticity in the lower limbs with a bilateral Babinski sign, but brisk abdominal reflexes.

The subcortical centers seemingly control all motor activities in animals with a rudimentary cerebral cortex. As the cerebral cortex evolved in higher animals, many of the functions of the basal ganglia were taken over by it. Normally, both the old and the new motor system appear to cooperate; they are not antagonistic.

When man assumed the erect posture and the forelimbs no longer were needed for walking, the cerebral cortex attained its greatest development. The subcortical centers were still in control of all routine motor activities. The dominance of the frontal lobe evolved when the ability to grasp with the forelimbs developed. The corticospinal system is not a locomotor one, but makes possible newer functions—refined unilateral movements, dexterity, the planning and premeditation of actions and the element of deliberation, volition or intention. In hemiplegia with spastic paralysis, hyperreflexia, absence of superficial reflexes and the presence of the Babinski sign other pathways than those originating in the motor cortex are involved. This clinical picture is due to lesions of a number of fiber tracts, among them the corticospinal, or pyramidal, tract and other cortical and subcorticospinal tracts, all converging on the anterior horn cells in their common function, the production of the forms of normal motor activity possessed by man. Destructive pathologic lesions, such as occur in vascular disease, may affect all these fiber tracts, whereas the types of pathologic change associated with amyotrophic lateral sclerosis are more selective and interrupt some of the fibers, at the same time permitting others to function normally. Thus the abdominal reflexes may be present despite spastic paralysis with the Babinski sign and hyperreflexia.

Involuntary movements are attributed to lesions of the basal ganglia, with release of other centers, thus permitting the movements to appear. Stimulation of intracranial structures has not resulted in reproduction of abnormal involuntary movements comparable to those present in syndromes of the basal ganglia. Convulsive seizures differ from these abnormal involuntary movements in that they result from disturbed function of the cerebral cortex, can be reproduced by experimental stimulation of the cortex and occur during sleep. Movements due to lesions of the basal ganglia cease when the patient is asleep. Seemingly, such movements are abolished when consciousness is interrupted and recur immediately when consciousness is restored. These various forms of molecular displacements enter and

traverse the sensory pathways. Before they reach the descending corticospinal and/or subcorticospinal pathways, important alterations take place. If this were not so, all animal life would appear in a state of disorder and unrest, similar to that observed in the universe of inanimate objects, and to which has been applied the designation "brownian movement." Because the basal ganglia interrupt and modify the stream of these molecular displacements, the normal, synchronized, smooth motor functions present in all animal life are made possible. When any of these basal ganglia do not function normally there passes through them, onto and down the descending motor pathways those original, unaltered, involuntary movements, and alterations in tonus, resulting in the clinical syndromes that have been regarded as typical of basal ganglia disease, then appear.

DISCUSSION

DR. FREDERICK A. METTLER (by invitation): As I understand Dr. Rabiner's concept, abnormal movements are of two types: epileptiform discharges, which can be produced by stimulation and which occur in sleep, and dyskinesias of the type called extrapyramidal; these do not occur in sleep, nor does stimulation produce them. Epileptiform discharges may be produced by, or stimulated by, a variety of things, and Dr. Rabiner might have mentioned experiments which have been made at the New York State Psychiatric Institute. Why is it that one type of abnormal movements always disappears in sleep while the other does not? Dr. Rabiner made an important point when he said that the former type is based on some disorder in the neurologic conduction of essentially normally arising impulses, whereas the latter type represents discharges which may be considered to arise *de novo,* and in an abnormal manner. He emphasized his point by mentioning the exacerbation of extrapyramidal disease by emotional states. I believe that Dr. Rabiner has become entangled in the use of such terms as "molecular disorders" and "brownian movement"; I do not see the meaning of these terms in the present connection. The brownian movement is an extraordinarily rapid phenomenon; it is difficult to see. It is observed, as a matter of fact, only as agitation of a very small mass. It would be difficult to conceive of it as movement of any appreciable mass. I suggest that analogies of this sort would best be left out. However, to get to more specific matters, and ones on which some of us may share Dr. Rabiner's opinion: There is an old story about a patient with paralysis agitans who became hemiplegic and the paralysis agitans disappeared. Such a thing happens; indeed, it is the rule, but it is the exception to the rule which is enlightening. If it always occurred, one might be forced to unjustified conclusions. If all patients who have paralysis agitans and who become hemiplegic lost all their abnormal movement, one might assume, as Dr. Putnam did, that the corticospinal tract is the pacemaker for the abnormal movement. In such circumstances, one would need only to cut the tract in order to abolish the movement. As a matter of fact, abnormal movements of this type may occur in the complete absence of the corticospinal system. With Grimes and Davidoff, I reported a case of that sort. In that case the peduncular system was completely cut off, and yet the patient continued to have movements of the type which were diagnosed by others as typical of paralysis agitans.

I should like to refer to another point: the statement that the corticospinal system, or the pyramidal system, has its origin in the motor cortex and its efferent pathway in the pyramidal tract. This has been the subject of considerable laboratory work in the past decade, but the results have not reached the clinical texts, which are still obfuscated. The facts are these: Of the number of fibers which

make up the corticospinal tract, from 5 to 3 per cent only can arise from the Betz cells. Where do the rest come from? Do some of them, as Dr. Rabiner says that Monakow and Swank asserted, arise from subcortical regions? That idea dates back to Marie and Guillain, who called this hypothetic path the parapyramidal system, and it has cropped up from time to time.

It must be understood that the term "pyramidal tract" refers to fibers passing through the pyramids of the medulla and does not imply that it contains fibers arising from the pyramidal cells of the cortex. The truth is that there are no fibers in the pyramids which arise anywhere but in the cortex. Now, where do the fibers come from if not from the Betz cells? A large number of them come from area 4; all the larger ones do, but there are still about 60 per cent which cannot come from there. Some, the smaller fibers, come from area 6. Do any arise elsewhere? Apparently, they do. Work by Marshall, Woolsey and Peale, and also by Monakow, indicated that fibers descending in the pyramids probably come also from the parietal lobe. They may come also from the cortex lying farther caudally, or even from the cortex rostral to area 6. In summary, there are no fibers in the pyramid which are not cortical in origin. Not many fibers in the pyramidal tract come from Betz cells. Many come from area 4; there are also fibers which come from rostrally and caudally situated areas.

Do animals devoid of cortex have no conditioned reflexes as Dr. Rabiner has stated? The idea that the conditioned reflex is a special function of the cerebral cortex originated with Pavlov as a purely speculative extension of work by Zeliony, who later tried to repeat his work. Why did he try to repeat it? One would assume that he distrusted Pavlov's conclusions, and it is significant that he changed the method of obtaining the conditioned reflex. Originally Pavlov had had him use an autonomic reflex. When he tried to repeat the work, he used the Bechterevian somatomotor conditioned reflex. The fact is, as subsequently shown by my associates and me, that one can produce a conditioned reflex of a distorted kind if no cortex is present. Learning is by no means the special function of the cerebral cortex.

Does the frontal lobe arise as a special development of the ability to grasp, as Dr. Rabiner suggests? A study of the comparative anatomy of animals such as Ailuropoda melanoleuca (the giant panda), the kangaroo (of which I am reminded by seeing our guest from Australia) or the raccoon, animals which all have grasp and yet possess a frontal lobe very similar to that of the carnivores, which do not have grasp, shows that the correlation is far from obvious.

Again, is voluntary movement a function peculiar to the cerebral cortex? Animals that have no cortex appear to have voluntary movement; perhaps the question is a semantic one.

I wonder whether the descriptive material with regard to dyskinesias is always unequivocal. I have recently had several workers in the laboratory examine the literature on extrapyramidal movements of various types. The greatest obstacle to an evaluation of this sort is that the authors have used different descriptive diagnostic criteria. My colleagues and I have finally been forced to believe that the only way we can tell what an author means is to have him send a moving picture; then we can tell.

There is a point which the neurosurgeons might think about. Is it true that section of the various portions of the neuraxis which produces improvement in extrapyramidal disease always owes that improvement to the development of a paralysis? It certainly is true that many of the surgical procedures do produce paralysis, and so make the matter a difficult one to settle; but one suspects that

if the operation is done carefully the degree of paralysis is minimal. One feels that the amount of improvement is not proportionate to the degree of paralysis.

DR. ABRAHAM M. RABINER: With regard to the brownian movement, I am not a physicist, but when I became interested in this phenomenon I discussed the matter with many physicists. They tell me, and the literature states, that the seeming quiet and restfulness which is present about us is an optical illusion, that actually there is a constant state of restlessness, that gravity is pulling us down to the ground and atmospheric pressure is pushing us down and that from all sides we are being bombarded by molecular displacements, a condition which would keep us in a constant state of movement. The only analogy I could find to this was the brownian movement. If we did not have a mechanism in the central nervous system to neutralize these molecular displacements, we should be in a constant state of quiver, such as occurs in the brownian movement.

Dr. Mettler speaks of the relation of the corticospinal system to tremor. I have never seen a case in which there was any arrest of the tremor of parkinsonism unless at least a modicum of weakness was demonstrable in the part affected. Certainly, that pathway which the surgeon sections, or the cortex which he excises, does not result in the type of movement which is influenced by the operative procedure; that pathway has nothing to do with the movement itself except that through it pass influences which permit the tremor to occur, and those influences arise elsewhere than in the pathway.

Some of the lower animals may have a type of grasp, but I am concerned with the concept of the frontal lobe coming into its own, so far as it functions in man. This must have occurred at a time when the primitive animal realized that this ability to grasp enabled him to hold and use a weapon against another animal which had previously dominated him, and so was prompted to the planning of a future attack.

Spreading Depression of Electrical Activity in the Cerebral Cortex Following Local Trauma and Its Possible Role in Concussion. DR. FRANCIS A. ECHLIN.

A localized mechanical stimulus to the cerebral cortex of rabbits insufficient to cause irreversible injury gives rise to a phenomenon designated by Leao and associates as spreading depression (*J. Neurophysiol.* **7**:369, 391, 1944; **8**:33, 1945; **10**:409, 1947). At the point of stimulation there occurs a marked decrease in the spontaneous electrical activity of the cortex, especially potentials of the faster frequencies. This depression of electrical activity then spreads outward to involve almost the entire ipsilateral cortex in about five minutes. During the spread of the depression large, slow waves appear over both hemispheres. The entire process is reversible, the normal cortical activity returning in approximately twenty minutes.

Spreading depression of electrical activity in the human cerebral cortex, apparently similar to that observed in rabbits, has been recorded after the insertion of a ventricle needle into the occipital lobe during ventriculography. The depression of activity is not so pronounced in the human cortex as in the rabbit's, and return of normal activity is usually evident over the temporal area by the time the depression has spread to the frontal regions of the head.

A blow to the head of sufficient force to cause concussion would be expected to provide a stimulus to nerve tissue adequate to set up spreading depression from innumerable points in the cerebral cortex simultaneously. Actually, there is a striking similarity between the electroencephalographic findings in rabbits subjected to "spreading depression" and those shown by Williams and Denny-Brown (*Brain* **64**:223, 1941) to follow experimental concussion [lantern slides].

Conclusions.—It is suggested that the electroencephalographic findings in cases of concussion may be largely explained on the basis of a "spreading depression" of electrical activity initiated simultaneously from innumerable points in the cerebral cortex.

The phenomenon of spreading depression might in itself be responsible for a disturbance or loss of consciousness following a blow to the head, and it may be initiated by a stimulus inadequate to cause irreversible injury.

DISCUSSION

DR. MARGARET RHEINBERGER (by invitation): Dr. Echlin's slides portrayed graphically that there is such a thing as spreading depression in situations of injury directed against the brain, as well as in situations of gross injury directed against the closed skull. This similarity of reaction in the two situations stands up very well with the results of Williams and Denny-Brown and their observation of the depression which followed concussion in animals. Perhaps it might be of benefit if I recalled that in Williams and Denny-Brown's experiments with concussion the animals showed at the time of the injury reflex inhibition, loss of the corneal reflex and respiratory and circulatory changes, effects similar to those which Dr. Echlin has described as accompanying concussion in man. Thus, both the electrical and the physical changes occurring with concussion may be similar in man and in animals.

I think that Dr. Echlin means to emphasize that the electric phenomenon, which is reversible when the blow is not too severe, is a possible physiologic basis for effects accompanying injury in man, changes which may take place without any demonstrable anatomic change in the brain itself. The mechanism by which these electrical effects are produced has been investigated extensively by Leao and others, with no conclusion as to the chemical, vascular or other factors which are the specific initiating source of the changes; but the fact that changes in the brain accompanying a traumatic situation have been demonstrated gives, perhaps, a little assurance that injury really has taken place, even though it cannot be shown histologically.

DR. BARRY WYKE, Sydney, Australia (by invitation): This problem of Dr. Echlin's is related to one on which my colleagues and I have been working for some time, and his results are very interesting. I should like to bring out one or two points which may be germane, realizing that marsupials and rabbits have become an Australian prerogative as experimental animals (I thank Dr. Mettler for his reference to kangaroos). The phenomenon of the spread of slow activity in the rabbit brain has been extensively studied both in America and in Australia, and it is unfortunate that the electrical changes which occur in the cortex of the rabbit are often different from those which occur in the cortex of cats, dogs, monkeys and human beings. It has been found that the slowly spreading depression of electrical activity in the rabbit is probably associated with changes in the direct current potentials which have been shown to exist between the ventricle and the cortex of such animals as the frog and the rabbit. In the brains of these particular animals spreading depression resembling that described by Leao is associated with a slow oscillation of the pial-ventricular potential. We have not been able to demonstrate any such phenomenon in cats, dogs, monkeys or man, and that is why I was very much interested in these records of Dr. Echlin. However, we have been able to demonstrate in each of the aforementioned species, including man, the phenomenon of cortical suppression as described by Dusser de Barenne

and his school, but this has (in unanesthetized human subjects, at least) a shorter time course than the phenomenon of Leao and that shown in Dr. Echlin's records, and does not have the associated vascular changes.

One or two difficulties occur to me, particularly the frequency response of the amplifiers employed by Dr. Echlin, a critical point in the recording of such slow changes in potential as these. I wonder, also, whether Dr. Echlin has been able to demonstrate in the human cortex the phenomenon of cortical suppression (described in the cat by Dusser de Barenne and in man by me), as distinct from Leao's phenomenon. According to present knowledge, four phenomena can be elicited in the cerebral cortex: depression, extinction, suppression and inhibition, and they all differ in their mutual time relations. We have never been able to demonstrate spreading depression in the primate cortex, although it is easily found in the rabbit; yet we have been able to demonstrate cortical suppression in all the animals we have examined, as well as in man. What the relation of these phenomena may be I cannot say, but Dr. Echlin's records of spreading depression in the human brain are extraordinarily interesting, since they are in direct contrast to our own unsuccessful experience in trying to demonstrate in man.

It is also important to know whether the patient was under the influence of any anesthetic or preoperative drug, for it is well known that the passage of the direct current potential across the animal cortex is influenced by many such drugs.

Finally, I should like to thank Dr. Brock for his invitation to discuss these interesting results obtained by Dr. Echlin.

DR. FRANCIS A. ECHLIN: The patient had had local anesthesia; he had had about 2 grains (0.13 Gm.) of phenobarbital sodium U. S. P. before he came to the operating room, and the depression was set up by inserting a ventricle needle into the occipital lobe on that side.

Electric Current and Metrazol® as Aids in the Diagnosis of Epilepsy. DR. THEODORE MELTZER and (by invitation) DR. E. LOUIS REDER.

In an effort to be more objective in the diagnosis of epilepsy, the authors studied 28 patients with grand mal epilepsy, verified by observation. Each patient was subjected to two tests: (1) intravenous injection of 1 cc. of 10 per cent metrazol® and (2) application of electricity to the temporal regions of the head (60 and 70 volts for 0.2 second). It was found that 4 patients responded with a grand mal convulsion to the 1 cc. of 10 per cent metrazol®; 5 patients responded with a grand mal convulsion to 60 volts of electricity for 0.2 second, and 5 other patients responded in a similar manner to 70 volts for 0.2 second. Since the amounts of metrazol® and electricity used were far below the amounts required to produce such a reaction in normal persons, as indicated in the literature and by the results in 28 nonepileptic (psychoneurotic) subjects used as controls, it was felt that the results were significant. It was proposed that this method is a simple test for grand mal epilepsy, valuable especially when the electroencephalogram is not conclusive. The value of the test is limited only to positive results, since a negative result does not rule out epilepsy. For electric stimulation, the machine must be well standardized with normal controls before it is used for the purposes outlined. The only requirement for metrazol® is that it be injected as rapidly as possible.

DISCUSSION

DR. MATTHEW BRODY (by invitation): The work of Dr. Meltzer and Dr. Reder is an important confirmation of previously reported studies. There is no question that epileptic persons as a group, statistically speaking, have a lower

convulsion threshold than have so-called normal persons, whether this is tested by hyperventilation, the combined pitressin®-hydration test or by metrazol® or the electric current, as in this test. How significant such a finding might be in any single case is a different matter. I should like to point out that young schizophrenic patients (under 18 years of age) who are exceedingly frightened and anxious, but who show no clinical evidence of epilepsy, may have convulsions with currents which Dr. Meltzer and Reder seem to believe pathognomonic for epilepsy. I think that one may conclude that the test which these authors propose may give some indication of the convulsion threshold of a person at a particular time. Epilepsy, however, is dependent on at least two variable factors: (1) the presence of focal firing points and (2) a lowered convulsion threshold. This test gives some indication of one of these factors, a low convulsion threshold, which in itself may be strongly indicative, but not necessarily pathognomonic, of epilepsy. However, in view of this excellent study, persons given convulsion shock therapy should study those patients showing unusually low (and perhaps also unusually high) convulsion thresholds.

Dr. Lothar B. Kalinowsky: I should like to comment on how far withdrawal of the anticonvulsive drug before electric shock treatment may be responsible for the lower threshold. My own experiments with electric shock therapy of epilepsy has made me doubtful whether epileptic patients actually have a lower threshold. Withdrawal, particularly of barbiturates, lowers the threshold considerably, as evidenced by so-called withdrawal seizures in nonepileptic patients.

Considerable work has been done showing rather contradictory results for these tests, especially with metrazol.® I should like to know whether the authors have tried withdrawal of anticonvulsive drugs for several months before making the test.

Dr. Theodore Meltzer: The drug was withdrawn at least two weeks before the onset of the experiment. Since the experiment ran for three and a half months, some of the patients had a longer withdrawal period than others. None of our patients was observed for seven or eight months after withdrawal of the drug and prior to administration of the electric current or metrazol.®

CHICAGO NEUROLOGICAL SOCIETY

Alex J. Arieff, M.D., *President, in the Chair*

Regular Meeting, Oct. 11, 1949

Metabolism of the Isolated Functioning Spinal Cord. Dr. R. W. Gerard, Dr. R. D. Tschirgi, Mr. H. P. Jenerick and Dr. J. Z. Hearon.

A correlated study of function and metabolism is clearly most valuable in illuminating normal and abnormal processes in the nervous system. Such combined measurements become possible in rigorous fashion on a nervous system functioning in vitro. We have developed a preparation of the completely isolated rat spinal cord which maintains essentially normal reflex activity for several hours.

The thoracic or lumbar cord is exposed by laminectomy; the chest is opened under artificial respiration; the abdominal aorta and major branches are ligated and the arch is cannulated, and perfusion is started. The desired segments of cord and vertebral bodies are then excised, the lateral cuts being sealed by electrocautery. The bone is then fixed in dental cement and the cord covered with oil. An appropriate pump gives the desired mean and pulse pressures and pulse rate.

Both solution and cord are kept at 37 C. by thermistor regulators. Tyrode solution, with protein and 100 mg. of dextrose, and saturated with a mixture of 95 per cent oxygen and 5 per cent carbon dioxide, with hemoglobin or protein and red cells, is a satisfactory perfusion fluid. The rates of perfusion are normally slow enough that a second circulation is not necessary and the total perfusate can be collected for chemical analysis. A dorsal root is stimulated at a frequency of 20 per second, and the height of the monosynaptic spike on the ipsilateral ventral root is measured for reflex activity.

The perfusion rate, determined by the cord, varies fivefold (1 to 5 cc. per gram of cord per minute); the use of dextrose (7.4 mg. per gram of cord per hour) and of oxygen (4,200 cu. mm. per gram of cord per hour) vary only 10 to 12 per cent over all complete experiments. The respiratory quotient is 0.99. If oxygen or dextrose is omitted from the perfusion fluid, the reflex is lost in 1 to 2 or 2 to 4 minutes, respectively; when restored, even 30 minutes later, the reflex response recovers fully. Forty-five or 50 mg. of dextrose per hundred cubic centimeters keeps the reflex full strength; 40 mg. per hundred cubic centimeters is as ineffective as no dextrose. Many substances, including succinate, which is rapidly used by the cord, fail to replace dextrose in supporting function. Pyruvate, isocitrate, glutamate and alpha ketoglutaric acid, however, can fully substitute for dextrose. These findings permit significant conclusions concerning neural metabolism.

Electrical Excitation of the Cerebral Motor Cortex with Varying Parameters of Stimulation. DR. THEODORE RASMUSSEN and DR. CHARLES CURE.

Electrical stimulation of the cerebral motor cortex was carried out on 15 monkeys with special reference to form, frequency and intensity of the exciting current. It was found that at a given point on the cortex deviation of the motor response occurred with alteration in the frequency of both square wave and sine wave currents. In general, distal movements tended to occur with slower frequencies, and proximal movements, with faster ones. With square wave stimuli at a given frequency, but with varying pulse lengths, the motor response was frequently constant, but occasionally deviation was noted; when this occurred, pulses of short duration favored distal movements, while pulses of longer duration favored proximal movements. It was found that points of deviation on the frequency scale could be altered by changing the position of the electrode on the cortex. Alterations in the depth of anesthesia, permitting spontaneous movements of the extremity or administration of concomitant afferent stimuli, also affected the response.

Leptomeningeal Changes in a Case of Lipochondrodystrophy (Gargoylism; Hurler's Syndrome). DR. KENNETH R. MAGEE.

A neuropathologic study was made on the central nervous system of a 29 month old child who presented all the typical clinical features of lipochondrodystrophy (gargoylism).

The most spectacular pathologic change was massive thickening of the pia-arachnoid over the convexity of the left cerebral hemisphere. Microscopic sections of this region revealed a dense mass of collagenous connective tissue, associated with the presence of large reticulated cells containing considerable quantities of lipid material. A large subdural hematoma on the lateral aspect of the right cerebral hemisphere was shown not to be responsible for the overgrowth of connective tissue. Similar hyperplasia of connective tissue associated with the presence of macrophages was noted throughout many other organs of the body.

Though postmortem changes precluded detailed accurate analysis of the changes in the brain and spinal cord, it was evident that there was widespread ganglion cell disease typical of that seen in lipochondrodystrophy. Routine stains for fat did not demonstrate lipid in these cells. However, small clusters of lipid-stained material in neurons of the cerebral cortex were demonstrated by the suprasaturated isopropanol method with oil red O.

A discussion of the changes in the central nervous system associated with lipochondrodystrophy was given, with a comparison of the author's findings with those of other investigators.

Tumors of the Spinal Cord in Infancy. DR. DOUGLAS BUCHANAN.

An attempt was made to establish a pattern for the signs and symptoms of tumor of the spinal cord occurring in infancy.

In 6 cases the diagnosis of tumor of the spinal cord was established by operation at the University of Chicago Clinics. All the children have survived. In 4 cases the tumor was extramedullary, and in 2, within the spinal cord.

In all the initial complaint was stiffness of the neck or back, weakness of the legs and pain on movement of the body. There were weakness and reduction of the deep reflexes in the arms and great weakness and increase in the deep reflexes in the legs. Absolute loss of appreciation of pinprick below a specific spinal level was not established. In the cases of intramedullary tumors sweating was absent on the body below the appropriate level.

In all 6 cases examination of the spinal fluid revealed a spinal block with great increase in the protein content of the fluid. In 5 cases a myelogram was made before operation.

Acute anterior poliomyelitis and amyotonia congenita are the diseases most easily confused in infancy with tumors of the spinal cord. If the deep reflexes are present in the legs, the diagnosis of amyotonia congenita cannot be supported. Even less is this possible if the deep reflexes in the legs are increased and the plantar responses conspicuously extensor. For the same reasons, acute anterior poliomyelitis is excluded. The demonstration of even a relative sensory level excludes both diagnoses. The absence of sweating in the lower portions of the body is evidence of an intramedullary lesion. A history of episodes of weakness of the limbs with periodic partial recovery is suggestive of an extramedullary cystic tumor.

Effects of Temporary Occlusion of the Middle Cerebral Artery in the Macaque Monkey. DR. THEODORE RASMUSSEN and DR. JOHN HARVEY.

The right middle cerebral artery was occluded in 9 animals permanently and in 12 animals for periods of from ten to fifty-two minutes. A continuous electrocorticogram was obtained during the procedure, and periodic records were taken from the scalp afterward. The survival periods following temporary occlusion varied from fifteen to eighteen days. The infarcts were studied grossly and microscopically. The results were summarized as follows: 1. No permanent clinical change resulted from occlusion of less than fifteen minutes' duration. 2. No gross cortical infarction resulted from occlusion of less than thirty minutes' duration. 3. Motor impairment as severe as that following permanent occlusion did not result from any occlusion of less than fifty minutes' duration. 4. Occlusion of fifty minutes' duration did not produce as extensive an infarct as that usually associated with permanent occlusion.

The electroencephalographic findings will be discussed in a later report.

Alex J. Arieff, M.D., *President, in the Chair*

Regular Meeting, Nov. 8, 1949

Vascular Malformations of the Scalp: Report of Two Cases. Dr. I. J. Speigel and Dr. Jordan L. Daniels.

The salient diagnostic features of cirsoid aneurysm and sinus pericranii were presented in 2 cases encountered in the neurosurgical service of the Michael Reese Hospital. These represented the two recognized types of vascular malformations of the scalp.

Frequent headaches and grand mal seizures were seen in the case of sinus pericranii. The lesion consisted of a large, spongy mass, composed of venous channels involving the entire thickness of the scalp and eroding the underlying bone. Intracranial vascular communications were also noted.

The cirsoid aneurysm did not differ from the usual arteriovenous aneurysm. A palpable thrill and bruit disappeared when the main feeder arteries were occluded digitally.

The accepted surgical treatment is total extirpation of both lesions. In sinus pericranii the intracranial communications are plugged with bone wax. The main feeder arteries to the cirsoid aneurysm are ligated initially, and then the lesion is resected.

Occlusion of the Superior Cerebellar Artery. Dr. Joseph A. Luhan and Dr. Seymour L. Pollock.

Five cases of this unusual vascular insult were presented. In the first 3 cases the lesion was clinically obvious, but without confirmation by necropsy. In each of these 3 cases, with ages ranging from 60 to 67, there was sudden onset of dizziness and inability to stand or walk. On one side there was intention tremor of the extremities and Horner's syndrome, and on the other, impairment or loss of pain and temperature sense, inclusive of the face.

In the fourth case, that of a man aged 29, neurologic symptoms developed during the course of subacute bacterial endocarditis. He presented intention tremor on the left side and subjective numbness of the right half of the body; in addition, there was nystagmus. Necropsy revealed occlusion of the left superior cerebellar artery with a somewhat unusual distribution of softening, which involved the brachium conjunctivum and the medial longitudinal bundle and largely spared the long sensory pathways for pain sense.

In the fifth case, that of a woman aged 38, two successive vascular lesions were presented, the first an occlusion of the right superior cerebellar artery, the second producing massive encephalomalacia in the distribution of the left middle cerebral artery. The symptoms resulting from the first occlusion were typical.

The symptoms following occlusion of the superior cerebellar artery arise from interruption of the brachium conjunctivum, the lateral spinothalamic and quintothalamic pathways, the descending oculosympathetic fibers and, sometimes, the lateral lemniscus and medial longitudinal bundle in the tegmentum of the rostral portion of the pons.

DISCUSSION

Dr. Joseph A. Luhan: In cases of occlusion of the superior cerebellar artery the major feature apparently is the neocerebellar disturbance due to involvement of the brachium conjunctivum. There is great variability of vascular supply

throughout the body, and occlusion of a superior cerebellar artery with an erratic distribution may produce a syndrome with distracting variations.

In this connection, I am reminded of the case of a soldier at Percy Jones Hospital whom I examined recently. The patient presented at the onset of his illness all the classic signs and symptoms of occlusion of the posterior inferior cerebellar artery except that, instead of crossed analgesia, he had total contralateral analgesia, including the face. It was shown by J. S. B. Stopford in 1916 and 1917, by injection experiments of vessels in the brain stem, that it is entirely possible for the posterior inferior cerebellar artery to irrigate the areas which supply the crossed spinothalamic and quintothalamic tracts lying in the retro-olivary reticular formation of the medulla, while not supplying the area occupied by the ipsilateral spinal tract and nucleus of the fifth nerve. With occlusion of the posterior inferior cerebellar artery with such a distribution, it is therefore possible to obtain total contralateral analgesia, and a case of this kind with necropsy control was reported by van Oordt in the *Deutsche Zeitschrift für Nervenheilkunde* in 1896.

There may be considerable recovery of function in cases of vascular occlusion of the brain stem. The soldier at Percy Jones Hospital had complete unilateral paralysis of the vocal cord, paralysis of swallowing and Horner's syndrome, which eventually disappeared, and at the time of this report there is only slight loss of pain sense in the contralateral distribution. Likewise, with occlusion of the superior cerebellar artery, the impairment of pain and temperature sense may largely recede, and the Horner syndrome may disappear.

Effect of Streptomycin on the Pathologic Lesions of Tuberculous Meningitis. Dr. Abraham Levinson, Dr. Joseph A. Luhan, Dr. William P. Mavrelis and Dr. Herbert Herzon.

The effects of streptomycin on the pathologic lesions in 26 cases of tuberculous meningitis, including 16 cases in which life was prolonged a minimum of thirty-five days, were studied. After prolonged therapy (a minimum of ninety days) advanced healing changes were observed in the miliary lesions in the viscera and in the exudate of the meninges. Notwithstanding, there were usually present caseous or incompletely healed miliary foci and unhealed foci in the meninges. The pathodynamics of healing of tuberculous lesions in the meninges and viscera under the influence of streptomycin is a process of diminishing cellularity and progressive fibroplasia.

In 2 cases we were unable to detect the presence of the primary tuberculous focus, and we presume that this focus healed without leaving demonstrable evidence of its former presence. In addition, we observed well advanced healing in the primary pulmonary focus in 2 other cases.

In spite of prolonged streptomycin therapy, caseous foci, such as were noted in the primary pulmonary lesion and in the pulmonary lymph nodes, persisted in the majority of cases. These foci were assumed to be the sites of origin of repeated hematogenous disseminations of tubercle bacilli.

The following features of the brain in cases of streptomycin-treated tuberculous meningitis were frequent: (1) necrotic or ischemic softenings in the rostral basal ganglia on the side opposite the hemiparesis noted in life (31 per cent of cases); (2) a greater incidence of extreme degrees of internal hydrocephalus than that observed without the treatment; (3) selective involvement of the stem of the sylvian fissure by a thick granulomatous exudate, within which occurred endarteritis of branches of the middle cerebral artery supplying the basal ganglia,

an inflammatory change which was the cause of the ischemic softenings (areas of necrotizing tuberculous destruction of the basal ganglia appeared continuous with the inflammatory process in the stem of the sylvian fissure); (4) destruction (3 cases) of the falx cerebri by a necrotic exudate.

Relapses in cases of streptomycin-treated tuberculous meningitis were explained as usually the result of repeated miliary dissemination to the meninges from unhealed caseous foci in the body, and occasionally of a local breakdown of minute caseous foci within the meninges.

Definite healing of meningeal exudate can be effected without resort to intrathecal therapy, the streptomycin reaching the exudate by way of the meningeal capillaries. The mechanism of healing of the exudate, by the formation of a thick fibrous scar at the base of the brain, associated with endarteritis of arteries traversing the exudate, stands as an obstacle to uncomplicated cure in streptomycin-treated tuberculous meningitis.

DISCUSSION

DR. PERCIVAL BAILEY: Why did you not give the streptomycin intrathecally?

DR. VICTOR GONDA: This presentation dealt exclusively with pathologic changes, and there was no mention of possible improvement in the spinal fluid findings during the course of streptomycin therapy. Were there any? If there were, what kind of improvement did you notice?

DR. OSCAR SUGAR: The British have had a great deal of experience with tuberculous meningitis, the cases having been concentrated in a few great centers because of the facilities which are made available by the National Research Council in Great Britain. Their recent reports are definite in stating that all patients with tuberculous meningitis should be given streptomycin intrathecally. Their rate of relapse was no greater than that mentioned in this paper, and their mortality rate was much lower over a period of two or more years of adequate study. I realize that in many cases of meningitis we in this part of the country prefer not to give streptomycin or other medications intrathecally; like Dr. Bailey, I was curious as to why it was not done in these cases. The British point out the occurrence of hydrocephalus in some cases; necropsy revealed that death was due to hydrocephalus, and not to tuberculosis, in some cases. Sir Hugh Cairns has been interested in attempting surgical treatment of hydrocephalus by various devices, hoping to overcome this obstacle.

Dr. W. R. KIRSCHBAUM: Is there a relation between the ages of the children and the outcome of the pathologic process under streptomycin treatment? Did the 2 adults react differently than the children? Did all these patients show the same allergic reaction toward the tuberculous infection, and were there signs that the healing tendencies due to streptomycin showed individual differences?

DR. HERBERT HERZON: Dr. Bailey asked why we did not use streptomycin intrathecally. Our method of therapy of tuberculous meningitis, in which streptomycin is given only intramuscularly, is in direct contrast to that in vogue among Eastern clinicians. They persevere in giving antibiotics intrathecally, irrespective of the type of meningitis under consideration. We in the Midwest, especially at the Cook County Hospital, have perhaps been influenced by the almost pioneer work of Dr. Archibald Hoyne. Dr. Hoyne demonstrated as long ago as 1934 that excellent results could be achieved in the treatment of meningitis without resort to intrathecal therapy. This fact was first demonstrated with meningococcic antitoxin, and subsequently with sulfonamides, after the latter drugs were placed in general use. Most clinicians found that intrathecal use of the sulfonamides was

dangerous, and this practice was abandoned. Despite their administration solely by the oral and parenteral routes, good results were obtained in the treatment of meningitis with these drugs. With the introduction of penicillin, however, though good results were again achieved, the trend was reversed. This perhaps resulted from the observation that penicillin, and subsequently streptomycin, could be given intrathecally with less trepidation than could the sulfonamides. Nevertheless, excellent results, comparable to or better than those reported for intrathecal therapy, have been achieved in the treatment of the meningococcic and, more recently, the influenzal and the pneumococcic meningitides without resort to the intrathecal route of administration of these antibiotics. Perhaps Dr. Levinson, who had clinical charge of these cases, can better defend his choice, but I presume that he felt that tuberculous meningitis could be cured similarly without the intrathecal use of streptomycin. He was thus one of the earliest to treat tuberculous meningitis without intrathecal medication.

The literature presents little pathologic or experimental evidence actually substantiating the need for intrathecal therapy, and, on the other hand, little that it is not needed. In the cases previously reported by Dr. Levinson, in which intramuscular therapy alone was used, streptomycin levels in the spinal fluid as high as 320 micrograms per milliliter were achieved with the clinical dosage, with an average of 5 to 20 micrograms per milliliter. Thus, streptomycin does enter the cerebrospinal fluid in adequate concentration. Perhaps of considerable significance were two observations made in the study of our pathologic material. We noted that healing apparently occurred earliest, and subsequently to the greatest extent, in those portions of the exudate in the immediate vicinity of meningeal vessels, rather than in those distal portions which were in close proximity to the cerebrospinal fluid. Similarly, the greatest degrees of healing occurred not in those portions of the exudate in direct contact with the cerebrospinal fluid, the distal areas, but in that portion of the exudate adjacent to the brain parenchyma itself. In fact, the distal portions in contact with the cerebrospinal fluid usually exhibited the freshest and most unchanged appearance, with no evidence of any healing whatsoever. It would appear from these observations that the parenterally administered streptomycin coursing through the meningeal vessels contributes more to the healing tendency than the streptomycin in the cerebrospinal fluid. There should also be borne in mind Dr. Bailey's conclusion that antibiotics given intrathecally are not as innocuous as was once assumed. Dr. Bailey decries the use of intrathecal therapy and notes the frequent disabilities consequent to its use.

In answer to Dr. Gonda's question, Dr. Levinson has analyzed in a recent paper the changes in the cerebrospinal fluid which occur under the influence of streptomycin therapy. He noted that the cell count showed a rise after the beginning of streptomycin treatment and then a recession. The same was true of the protein level. The values for glucose were most unusual in that they rose quickly, then fell again and gradually returned to normal. In answer to the third question, we were unable to find any correlation between the age of the patient and the degree of healing or the degree or nature of the fibroplasia.

Book Reviews

La neuro-angiomatose encéphalofaciale: Syndrome hypothalamohypophysaire. By A. M. Larmande. Price, 400 francs. Pp. 150. Masson & Cie, 120 Boulevard Saint-Germain, Paris, 6e, 1948.

This small book is a thorough study of a rather rare condition, only about 200 cases having been described. The author is the chief of the ophthalmologic clinic at the faculty of medicine in Algiers, where he had an opportunity during the war to examine some 30,000 recruits. Among them he found 5 cases of encephalofacial neuroangiomatosis, 3 of which are described in detail.

The history of the development of knowledge of the disorder is detailed and the confused and complicated terminology discussed. The author adopts the term used in the title, which seems to be quite appropriate. The observations on 3 of his cases are given in detail, and the interesting fact is noted that they all concerned Europeans. No case was discovered among the native North Africans.

The clinical syndrome is discussed exhaustively, noting the nevus flammeus, the craniofacial hypertrophy, the mental troubles, the hydrophthalmos and the cortical calcification. The author agrees that the cerebral calcification occurs in the cortex and not in the walls of angiomatous vessels. The malady is congenital, but rarely familial, and a hereditary factor has not been proved.

In its complete form, encephalofacial neuroangiomatosis is an anatomoclinical entity, characterized by (1) angiomatosis of the skin, mucosa, choroid, meninges and brain; (2) hemicranial and facial hypertrophy; (3) localized cerebral aplasia with gliomatosis, and (4) cortical calcification, visible in roentgenograms. These manifestations are strictly unilateral and give rise to secondary troubles: oligophrenia, epileptic attacks, hemiplegia and glaucoma. Many incomplete forms are known, the various manifestations occurring isolated or in any combination. One of the best known is the Sturge-Weber combination of facial nevus, calcified cerebromeningeal angioma and glaucoma.

The first 80 pages contain the clinical study of the syndrome. This account is factual, detailed and clear. The next 20 pages are given over to a theoretic study of nosography, physiopathology and pathogenesis. This section contains a great deal of ill founded speculation, especially concerning a possible hypothalamohypophysial alteration. The brief vague statements of the author surely do not justify the subtitle: *syndrome hypothalamohypophysaire.* However, the author has very carefully kept these speculations apart from the clinical description, which retains its value as a very useful summary of present knowledge of this interesting syndrome.

The book has no index, but it does have an extensive and detailed bibliography, which is so often missing in French medical publications. It will be useful not only to ophthalmologists but also to neurologists.

PERCIVAL BAILEY.

Le cortex cérébral: Étude neuro-psycho-pathologique. By J. D. Ajuriaguerra, M.D. and H. Hécaen, M.D. Price, 1,250 francs. Pp. 413, with 49 illustrations. Masson et Cie, 120 Boulevard Saint-Germain, Paris, 6e, 1949.

This good-sized monograph does not merely outline the authors' conclusions concerning cortical function and connections, but gives a complete historical résumé of everything discussed. The material is presented under the following headings:

(1) general survey of cerebral localization; (2) the frontal syndrome; (3) the rolandic syndromes; (4) the corpus callosum syndrome; (5) the parietal syndrome; (6) the temporal syndrome; (7) the occipital syndrome; (8) aphasia; (9) apraxias and agnosias, with scheme for examination; (10) apraxias; (11) agnosias; (12) hallucinations in cases of cortical lesions.

At the end of each chapter is a good bibliography. There are also author and subject indexes.

The book is a thoroughgoing and detailed presentation of the entire subject of localization of cortical function. Not all the recent work, however, is included, and the authors have not themselves settled disputed points but, rather, have contented themselves with an exposition of all known points of view. There is entirely too much in this volume to be adequately covered in a review. Any one wishing a good perspective of the present status of French knowledge of cerebral localization will find it here.

Cerebral Localization: Outline of a Revision. By Leland B. Alford, M.D. Price, $3.50. Pp. 99. Nervous and Mental Disease Monographs No. 77. Nervous and Mental Disease, 70 Pine St., New York 5, 1948.

In a monograph of 98 pages, the author attempts to present a new concept of cerebral localization. After a survey of disputed points in cerebral localization, he calls attention to the "distance reaction." He reviews the diaschisis of von Monakow, "crossed aphasia" and "vicarious function of the opposite hemisphere" and outlines his own interpretation of physical "distance reaction." He states:

"The term 'distance reaction' is used to refer to a diffuse, invisible change in the tissues surrounding a cerebral lesion. The conception was advanced by the writer in an article in 1944. The nature of the change is not clear, but it would seem to be some alteration in the interstitial tissues that interferes with conduction along nerve fibers without destroying them or in fact interrupting conduction altogether. That this sort of interference, a mere diminishing of nervous impulses, should be possible is a novel assumption, but it seems to be the most logical deduction from the findings which will be described."

He then explains most of aphasia, agnosia and apraxia on a psychiatric basis and gives his summary and orientation, of which the first paragraph follows:

"In the preceding pages the entire field of cerebral cortical symptomatology —the aphasias, the agnosias, apraxia, and the frontal lobe syndrome—has been surveyed and re-interpreted in the new light of the principles of the distance reaction in tissues and psychiatric viewpoints. The result of this appraisal was that all the cortical syndromes resolved themselves into psychiatric mechanisms either existing alone or built around concomitant motor, sensory or visual disturbances. The syndromes are, therefore, not valid entities, but combinations of circumstances, the chief predisposing factor of which was found to be mental instability of varying degrees. As no real mental defect or lack was identified in these groups, it was concluded that none existed. The only valid mental defect due to a focal lesion that could be identified in the entire realm of cerebral symptomatology proved to be that which is variously designated as confusion, disorientation, clouding of consciousness and dementia."

He finally does arrive at some localization in that he places the lesion necessary for stupor and coma in the left thalamus.

It would seem to the reviewer that any one claiming to improve on the work of Hughlings Jackson, Henschen, von Monakow, Schilder and many others should have a much better acquaintance with the work of these men than appears from this monograph to be possessed by the author.

Clinical Electroencephalography. By Robert Cohn. Price, $14. Pp. 639, with illustrations. New McGraw-Hill Book Company, Inc., 330 W. 42d St., New York 18, 1950.

The results of integration of the clinical and electroencephalographic findings in approximately 10,000 cases are reported. The subject material is presented in the form of an atlas. Interpretation of the electroencephalographic pattern and pertinent clinical data are presented opposite adequate samples of the original record.

A short, but adequate, discussion of the electroencephalogram is followed by examples of the normal pattern and its variations. The distribution of normal (85.6 per cent) and abnormal (14.4 per cent) patterns for subjects without neurologic disease is confirmatory of previous reports.

The incidence of electroencephalographic abnormalities associated with cerebral neoplasms, cerebrovascular disease, traumatic injuries to the brain (old and new) and epilepsy are essentially the same as that found with other types of similar material. Return of the electroencephalogram to normal after traumatic lesions, accidental or induced, is similar.

Included in the technic of recording brain waves at the naval hospital at Bethesda, Md., is a "sleep record." The author stresses the irregularity of the pattern during sleep and caution in its interpretation.

Headaches and migraine were studied separately. The classic migraine syndrome is accompanied with an incidence of abnormalities in the electroencephalograms of 41 per cent. In contrast, the electroencephalographic pattern in "headache" was largely dependent on the underlying cause, it being normal in only 5 per cent less of this group than of the control group.

A higher incidence of abnormal electroencephalograms was found in a group of patients with narcolepsy. The pattern was a nonspecific one.

A discussion of the electroencephalogram of patients with behavior disorders showed an incidence of normal patterns of 64.0 per cent. Examples of the electroencephalogram associated with anxiety states, psychopathic personality and problem children are included in this section. However, the author states, "patients who present classical histories of psychopathy, satisfactory to any school of thought, nevertheless, may show E. E. G. tracings that in no way can be considered abnormal."

This book, though similar to other publications, is an asset in the progress of interpretation of the electroencephalogram. A medical library will be more complete with than without it. It is recommended for clinical or reference purposes.

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